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METHOD OF PREPARATION OF HETEROCYCLIC MOLECULES WITH PHARMACEUTICAL, PHARMACEUTICAL EXCIPIENT, COSMECEUTICAL, AGROCHEMICAL AND INDUSTRIAL USES

BACKGROUND OF THE INVENTION

This invention pertains to processes that have utility in the construction of racemic and optically pure heterocyclic molecules that are to be screened for biological activities that would render them useful as pharmaceuticals, cosmeceuticals, pharmaceutical excipients or agrochemicals. More specifically, it pertains to the use of Ring-Closure olefin Metathesis (RCM) and Enzymatic Resolution (ER) for the production of optically pure synthetic intermediates during an organic synthesis and methods for elaboration of same.

BACKGROUND INFORMATION

Carbohydrates or saccharides are highly functionalized biomolecules present in plant and animal cells and tissues. These molecules play a key role in energy storage, cellular signaling and molecular recognition. Carbohydrates are critical in the early stages of inflammation and immune response and contribute to the progression of a number of diseases. In general, saccharides are poor therapeutic agents. These compounds are rapidly metabolized in the gut or the plasma and have low binding affinities to their targets. In addition, carbohydrates are difficult to synthesize and purify by conventional methods. The combination of the above drawbacks has considerably limited the use of saccharides as pharmaceuticals, cosmeceuticals, pharmaceutical excipients or agrochemicals. Such difficulties maybe overcome by the use of "carbohydrate mimetics" or optically active heterocyclic molecules that resemble carbohydrates but have improved stability, target affinity and synthetic availability.

One strategy for increasing the stability of carbohydrate mimetics is to replace the heteroatom anomeric linkage of the carbohydrate ring system with a non-heteroatom linkage. Traditionally, these carbohydrate mimetics have been prepared by direct cleavage of the anomeric carbon-oxygen bond with a hydride equivalent, as set forth in Rolf, D. et al J. Amer. Chem. Soc. 1982, 104, 3539-3541. Such transformations are

commonly carried out by reaction of the alkyl or acyl glycoside with a strong Lewis acid such as boron trifluoride etherate (BF_3•Et_2O), trifluoroacetic acid (CF_3CO_2H) and/or trimethylsilyl trifluoromethanesulfonate ($TMSOSO_2CF_3$) in the presence of an ionic hydride donor such as a trialkylsilane (Figure 1). Said carbohydrate mimetics have also been prepared by direct cleavage of the anomeric carbon-oxygen bond with a cyanide equivalent, as set forth in Martin, J. et al Tetrahedron Lett. 1998, 39, 5927-5930. Such transformations are commonly carried out by reaction of the bromoglycoside with a free radical initiator (e.g. AIBN) in the presence of an alkyl isocyanide (Figure 1). The use of trialkylsilyl cyanides for the preparation of cyano glycosides has also been described as set forth in Igarashi, Y. et al Bioorg. Med. Chem. Lett. 1997, 7(5), 613-616.

Such methodologies ultimately depend on the availability of the glycoside and are thereby limited in scope. Another drawback of the existing art is that the cleavage of the anomeric carbon-oxygen bond is not stereospecific and usually yields a mixture of stereoisomers. As such, there is an obvious and immediate need for novel methodology that provides rapid access to large quantities of optically pure heterocyclic molecules such as those set forth in this invention.

SUMMARY OF THE INVENTION

Relative to traditional methods, efficiency is introduced into the syntheses of these carbohydrate mimetics by combining starting materials according to formulae **A** and **D**, or formulae **B** and **E**, to provide esters according to formula **C**. Compounds according to formula **C** can then react with aldehydes according to formula **F** to provide acyclic intermediates according to formula **G**. Application of a stereoselective Ring Closure olefin Metathesis (RCM) reaction to compounds according to formula **G** provides the 3,6-dihydro-2H-pyrans according to formulae **H** or **I**. These intermediates are subsequently transformed into optically pure stereoisomers via enzymatic resolution (Scheme 1). It is to be understood that the transformation of compounds according to formula **G** to optically pure compounds according to formulae **H** or **I** can also be carried out by way of an enantioselective Ring Closure olefin Metathesis (RCM) reaction.

Efficiency is also introduced into the syntheses of these carbohydrate mimetics by reduction of compounds according to formula **G** to compounds according to formula **W**. Subsequent reaction of compounds according to formula **W** with carbonyl compounds

according to formula **R** provides acyclic intermediates according to formula **X.** Application of a stereoselective Ring Closure olefin Metathesis (RCM) reaction to compounds according to formula **X** provides the 3,6-dihydro-2H-pyrans according to formula **S** (Scheme 2). It is to be understood that the transformation of compounds according to formula **X** to optically pure compounds according to formula **S** can also be carried out by way of an enantioselective Ring Closure olefin Metathesis (RCM) reaction. When subjected to other synthetic transformations, compounds according to formula **H, I** and **S** provide a variety optically pure carbohydrate mimetics according to formulae **J, K, L, M, N, O, P, Q, T, U, V, Y** and **Z** (Figure 2).

One advantage of this method over existing state of the art is that it provides rapid access to large quantities of optically pure compounds according to formulae **H, I, J, K, L, M, N, O, P, Q, S, T, U, V, Y** and **Z**. Another advantage of this method is that it allows the introduction of a variety of substituents into compounds according to formulae **H, I, J, K, L, M, N, O, P, Q, S, T, U, V, Y** and **Z.**

In one aspect of this invention, said carbohydrate mimetics can be used to generate molecules or diverse compound libraries with potential pharmaceutical, pharmaceutical excipient, cosmeceutical, agrochemical or industrial applications.

In another aspect of this invention, said carbohydrate mimetics can be linked to polymeric supports and/or other molecules in order to generate diverse compound libraries with potential pharmaceutical, pharmaceutical excipient, cosmeceutical, agrochemical or industrial applications.

In still another aspect of this invention, said carbohydrate mimetics can be coordinated to metals in order to generate organometallic complexes or catalysts with potential pharmaceutical, pharmaceutical excipient, cosmeceutical, agrochemical or industrial applications as set forth in Kanai, M. et al Tetrahedron Lett. 2000, 41, 2405-2409; Groaning, M. D. et al Tetrahedron Lett. 1998, 39, 5485-5488; Bell, D. et al US 5,916,975 June 29, 1999; and RajanBabu, T. V. et al J. Org. Chem. 1997, 62, 6012-6028.

Accordingly, the present invention describes a process shown in scheme 3 for preparing pharmaceuticals, pharmaceutical excipients, cosmeceuticals or agrochemicals comprising:

1. An allylic halide reagent **A** is first reacted with an α-hydroxycarboxylic ester **D** forming an oxygen-carbon bond and forming ether **C**; alternatively, an allylic alcohol reagent **B** is first reacted with an α-substituted ester **D** forming an oxygen-carbon bond and forming ether **C**.
2. The resulting compound according to formula **C** is reacted in a subsequent synthetic step with an α,β-unsaturated carbonyl compound according to formula **F** forming a carbon-carbon bond and forming a compound according to formula **G**;
3. The resulting compound according to formula **G** is reacted with a ring-closing olefin metathesis (RCM) catalyst forming a carbon-carbon bond and forming substituted 3,6-dihydro-2H-pyrans according to formulae **H** or **I**.
4. The resulting compound according to formulae **H** or **I** is reacted with an enzyme producing the optically pure substituted 3,6-dihydro-2H-pyrans according to formulae **H** or **I**.
5. The resulting compound according to formulae **H** or **I** is reacted with an oxidant forming substituted tetrahydropyran according to formula **J**.
6. The resulting compound according to formula **J** is reacted with an enzyme or an electrophilic reagent producing the compound according to formula **K**.
7. The resulting compound according to formula **K** or alternatively the compound according to formula **J** is reacted under microwave radiation forming substituted bicyclo [3.2.1] lactone according to formula **L**.
8. The resulting compound according to formula **L** is reacted with a nucleophilic reagent forming substituted tetrahydropyran according to formula **M**.

It is to be understood that the process shown in scheme 3 applies to all stereoisomers of compounds **G**, **H**, **I**, **J**, **K**, **L** and **M**.

Accordingly, the present invention also describes a process shown in scheme 4 for preparing pharmaceuticals, pharmaceutical excipients, cosmeceuticals or agrochemicals comprising:

1. An allylic halide reagent **A** is first reacted with an α-hydroxycarboxylic ester **D** forming an oxygen-carbon bond and forming ether **C**; alternatively, an allylic alcohol reagent **B** is first reacted with an α-substituted ester **D** forming an oxygen-carbon bond and forming ether **C**.
2. The resulting compound according to formula **C** is reacted in a subsequent synthetic step with an α,β-unsaturated carbonyl compound according to formula **F** forming a carbon-carbon bond and forming a compound according to formula **G**;
3. The resulting compound according to formula **G** is reacted with a ring-closing olefin metathesis (RCM) catalyst forming a carbon-carbon bond and forming substituted 3,6-dihydro-2H-pyrans according to formulae **H** or **I**.
4. The resulting compound according to formulae **H** or **I** is reacted with an enzyme producing the optically pure substituted 3,6-dihydro-2H-pyrans according to formulae **H** or **I**.
5. The resulting compound according to formulae **H** or **I** is reacted with a reducing reagent forming substituted 3,6-dihydro-2H-pyran according to formula **N**.
6. The resulting compound according to formula **N** is reacted with an electrophilic reagent forming substituted 2,6-dihydro-2H-pyran according to formula **O**.
7. The resulting compound according to formula **O** is reacted with an epoxidation reagent forming substituted 3,7-dioxabicyclo[4.1.0]heptane according to formula **P**.
8. The resulting compound according to formula **P** is reacted with a nucleophilic reagent forming substituted tetrahydropyran according to formula **Q**.

It is to be understood that the process shown in scheme 4 applies to all stereoisomers of compounds **G**, **H**, **I**, **N**, **O**, **P** and **Q**.

Accordingly, the present invention also describes a process shown in scheme 5 for preparing pharmaceuticals, pharmaceutical excipients, cosmeceuticals or agrochemicals comprising:

1. An allylic halide reagent **A** is first reacted with an α-hydroxycarboxylic ester **D** forming an oxygen-carbon bond and forming ether **C**; alternatively, an allylic alcohol reagent **B** is first reacted with an α-substituted ester **D** forming an oxygen-carbon bond and forming ether **C**.
2. The resulting compound according to formula **C** is reacted in a subsequent synthetic step with an α,β-unsaturated carbonyl compound according to formula **F** forming a carbon-carbon bond and forming a compound according to formula **G**;
3. The resulting compound according to formula **G** is reacted with a ring-closing olefin metathesis (RCM) catalyst forming a carbon-carbon bond and forming substituted 3,6-dihydro-2H-pyrans according to formulae **H** or **I**.
4. The resulting compound according to formulae **H** or **I** is reacted with a reducing reagent forming substituted 3,6-dihydro-2H-pyran according to formula **N**.
5. The resulting compound according to formula **N** is reacted with an electrophilic reagent forming substituted 2,6-dihydro-2H-pyran according to formula **O**.
6. The resulting compound according to formula **O** is reacted with an epoxidation reagent forming substituted 3,7-dioxabicyclo[4.1.0]heptane according to formulae **P** or **Y**.
7. The resulting compound according to formulae **P** or **Y** is reacted with an enzyme producing the optically pure substituted 3,7-dioxabicyclo[4.1.0]heptane according to formula **P**.
8. Alternatively, the compound according to formula **N** is reacted with an epoxidation reagent forming substituted 3,7-dioxabicyclo[4.1.0]heptane according to formula **Z**.
9. The resulting compound according to formula **Z** is reacted with an enzyme producing the optically pure substituted 3,7-dioxabicyclo[4.1.0]heptane according to formula **P**.
10. The resulting compound according to formula **P** is reacted with a nucleophilic reagent forming substituted tetrahydropyran according to formula **Q**.

It is to be understood that the process shown in scheme 5 applies to all stereoisomers of compounds **G**, **H**, **I**, **N**, **O**, **P**, **Q**, **Y** and **Z**.

Accordingly, the present invention also describes a process shown in scheme 6 for preparing pharmaceuticals, pharmaceutical excipients, cosmeceuticals or agrochemicals comprising:

1. An allylic halide reagent **A** is first reacted with an α-hydroxycarboxylic ester **D** forming an oxygen-carbon bond and forming ether **C**; alternatively, an allylic alcohol reagent **B** is first reacted with an α-substituted ester **D** forming an oxygen-carbon bond and forming ether **C**.
2. The resulting compound according to formula **C** is reacted in a subsequent synthetic step with an α,β-unsaturated carbonyl compound according to formula **F** forming a carbon-carbon bond and forming a compound according to formula **G**;
3. The resulting compound according to formula **G** is reacted with a ring-closing olefin metathesis (RCM) catalyst forming a carbon-carbon bond and forming substituted 3,6-dihydro-2H-pyrans according to formulae **H** or **I**.
4. The resulting compound according to formulae **H** or **I** is reacted with a reducing reagent forming substituted 3,6-dihydro-2H-pyran according to formula **N**.
5. The resulting compound according to formula **N** is reacted with an electrophilic reagent forming substituted 2,6-dihydro-2H-pyran according to formula **O**.
6. The resulting compound according to formula **O** is reacted with an epoxidation reagent forming the optically pure substituted 3,7-dioxabicyclo[4.1.0]heptane according to formulae **P, Y** or **Z**.
7. The resulting compound according to formulae **P, Y** or **Z** is reacted with a nucleophilic reagent forming substituted tetrahydropyran according to formula **Q**.

It is to be understood that the process shown in scheme 6 applies to all stereoisomers of compounds **G**, **H**, **I**, **N**, **O**, **P**, **Q**, **Y** and **Z**.

Accordingly, the present invention also describes a process shown in scheme 7 for preparing pharmaceuticals, pharmaceutical excipients, cosmeceuticals or agrochemicals comprising:

1. An allylic halide reagent **A** is first reacted with an α-hydroxycarboxylic ester **D** forming an oxygen-carbon bond and forming ether **C**; alternatively, an allylic alcohol reagent **B** is first reacted with an α-substituted ester **D** forming an oxygen-carbon bond and forming ether **C**.
2. The resulting compound according to formula **C** is reacted in a subsequent synthetic step with an α,β-unsaturated carbonyl compound according to formula **F** forming a carbon-carbon bond and forming a compound according to formula **G**;
3. The resulting compound according to formula **G** is reacted with a ring-closing olefin metathesis (RCM) catalyst forming a carbon-carbon bond and forming substituted 3,6-dihydro-2H-pyrans according to formulae **H** or **I**.
4. The resulting compound according to formulae **H** or **I** is reacted with an enzyme producing the optically pure substituted 3,6-dihydro-2H-pyrans according to formulae **H** or **I**.
5. The resulting compound according to formulae **H** or **I** is reacted with a reducing reagent forming substituted 3,6-dihydro-2H-pyran according to formula **N**.
6. The resulting compound according to formula **N** is reacted with a carbonyl compound according to formula **R** forming substituted tetrahydropyran according to formula **S**.
7. The resulting compound according to formula **S** is reacted with an epoxidation reagent forming substituted hexahydro-1,3,5,7-tetraoxacyclopropa[a]naphthalene according to formula **T**.
8. The resulting compound according to formula **T** is reacted with a nucleophilic reagent forming substituted tetrahydropyran according to formula **U**.

It is to be understood that the process shown in scheme 7 applies to all stereoisomers of compounds **G**, **H**, **I**, **N**, **S**, **T** and **U**.

Accordingly, the present invention also describes a process shown in scheme 8 for preparing pharmaceuticals, pharmaceutical excipients, cosmeceuticals or agrochemicals comprising:

1. An allylic halide reagent **A** is first reacted with an α-hydroxycarboxylic ester **D** forming an oxygen-carbon bond and forming ether **C**; alternatively, an allylic alcohol reagent **B** is first reacted with an α-substituted ester **D** forming an oxygen-carbon bond and forming ether **C**.
2. The resulting compound according to formula **C** is reacted in a subsequent synthetic step with an α,β-unsaturated carbonyl compound according to formula **F** forming a carbon-carbon bond and forming a compound according to formula **G**;
3. The resulting compound according to formula **G** is reacted with a ring-closing olefin metathesis (RCM) catalyst forming a carbon-carbon bond and forming substituted 3,6-dihydro-2H-pyrans according to formulae **H** or **I**.
4. The resulting compound according to formulae **H** or **I** is reacted with an enzyme producing the optically pure substituted 3,6-dihydro-2H-pyrans according to formulae **H** or **I**.
5. The resulting compound according to formulae **H** or **I** is reacted with a reducing reagent forming substituted 3,6-dihydro-2H-pyran according to formula **N**.
6. The resulting compound according to formula **N** is reacted with a carbonyl compound according to formula **R** forming substituted tetrahydropyran according to formula **S**.
7. The resulting compound according to formula **S** is reacted with an oxidant forming substituted tetrahydropyran according to formula **V**.

It is to be understood that the process shown in scheme 8 applies to all stereoisomers of compounds **G, H, I, N, S** and **V**.

Accordingly, the present invention also describes a process shown in scheme 9 for preparing pharmaceuticals, pharmaceutical excipients, cosmeceuticals or agrochemicals comprising:

1. An allylic halide reagent **A** is first reacted with an α-hydroxycarboxylic ester **D** forming an oxygen-carbon bond and forming ether **C**; alternatively, an allylic

alcohol reagent **B** is first reacted with an α-substituted ester **D** forming an oxygen-carbon bond and forming ether **C**.

2. The resulting compound according to formula **C** is reacted in a subsequent synthetic step with an α,β-unsaturated carbonyl compound according to formula **F** forming a carbon-carbon bond and forming a compound according to formula **G**;
3. The resulting compound according to formula **G** is reacted with a ring-closing olefin metathesis (RCM) catalyst forming a carbon-carbon bond and forming substituted 3,6-dihydro-2H-pyrans according to formulae **H** or **I**.
4. The resulting compound according to formulae **H** or **I** is reacted with a reducing reagent forming substituted 3,6-dihydro-2H-pyran according to formula **N**.
5. The resulting compound according to formula **N** is reacted with a carbonyl compound according to formula **R** forming substituted tetrahydropyran according to formula **S**.
6. The resulting compound according to formula **S** is reacted with an oxidant forming optically pure substituted tetrahydropyran according to formula **V**.

It is to be understood that the process shown in scheme 8 applies to all stereoisomers of compounds **G**, **H**, **I**, **N**, **S** and **V**.

Accordingly, the present invention also describes a process shown in scheme 10 for preparing pharmaceuticals, pharmaceutical excipients, cosmeceuticals or agrochemicals comprising:

1. An allylic halide reagent **A** is first reacted with an α-hydroxycarboxylic ester **D** forming an oxygen-carbon bond and forming ether **C**; alternatively, an allylic alcohol reagent **B** is first reacted with an α-substituted ester **D** forming an oxygen-carbon bond and forming ether **C**.
2. The resulting compound according to formula **C** is reacted in a subsequent synthetic step with an α,β-unsaturated carbonyl compound according to formula **F** forming a carbon-carbon bond and forming a compound according to formula **G**;
3. The resulting compound according to formula **G** is reacted with a reducing reagent forming an alcohol according to formula **W**.
4. The resulting compound according to formula **W** is reacted with a carbonyl compound according to formula **R** forming a compound according to formula **X**.

5. The resulting compound according to formula **X** is reacted with a ring-closing olefin metathesis (RCM) catalyst forming a carbon-carbon bond and forming substituted tetrahydropyrans according to formula **S**.
6. The resulting compound according to formula **S** is then reacted according to schemes 7, 8 or 9 forming optically pure substituted tetrahydropyrans according to formula **T**, **U** and **V**.

It is to be understood that the process shown in scheme 8 applies to all stereoisomers of compounds **G**, **W**, **X**, and **S**.

Accordingly, the present invention also describes processes for preparing pharmaceuticals, pharmaceutical excipients, cosmeceuticals or agrochemicals comprising:

1. Compounds according to formulae **H, I, J, K, L, M, N, O, P, Q, S, T, U, V, Y** and **Z** can be linked to polymeric supports and/or other molecules in order to generate diverse compound libraries with potential pharmaceutical, pharmaceutical excipient, cosmeceutical, or agrochemical use.
2. Compounds according to formulae **H, I, J, K, L, M, N, O, P, Q, S, T, U, V, Y** and **Z** can be linked to metals and/or other metal containing molecules in order to generate diverse compound libraries with potential pharmaceutical, pharmaceutical excipient, cosmeceutical, or agrochemical use.
3. Compounds according to formulae **H, I, J, K, L, M, N, O, P, Q, S, T, U, V, Y** and **Z** can be linked to metals and/or other metal containing molecules and thereby serve as chiral catalysts in order to generate diverse compound libraries with potential pharmaceutical, pharmaceutical excipient, cosmeceutical, or agrochemical use.
4. Compounds according to formulae **H, I, J, K, L, M, N, O, P, Q, S, T, U, V, Y** and **Z** can be linked to achiral reagents and thereby serve as chiral auxiliaries in order to generate diverse compound libraries with potential pharmaceutical, pharmaceutical excipient, cosmeceutical, or agrochemical use.
5. Compounds according to formulae **H, I, J, K, L, M, N, O, P, Q, S, T, U, V, Y** and **Z** can be linked to other molecules and thereby serve as solubilizing agents in order to generate diverse compound libraries with potential pharmaceutical, pharmaceutical excipient, cosmeceutical, or agrochemical use.

6. Compounds according to formulae **H, I, J, K, L, M, N, O, P, Q, S, T, U, V, Y** and **Z** can be linked to other molecules in order to generate diverse compound libraries of prodrugs with potential pharmaceutical, pharmaceutical excipient, cosmeceutical, or agrochemical use.

Definitions

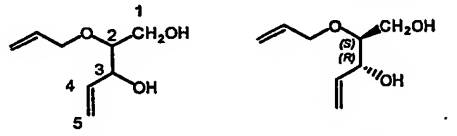
The compounds according to this invention contain one or more asymmetric carbon atoms and thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The term "stereoisomer" refers to a chemical compound having the same molecular weight, chemical composition, and constitution as another, but with the atoms grouped differently. That is, certain identical chemical moieties are at different orientations in space and, therefore, when pure, have the ability to rotate the plane of polarized light. However, some pure stereoisomers may have an optical rotation that is so slight that it is undetectable with present instrumentation. The compounds described herein may have one or more asymmetrical carbon atoms and therefore include various stereoisomers. All such isomeric forms of these compounds are expressly included in the present invention.

Each stereogenic carbon may be of R or S configuration. Although the specific compounds exemplified in this application may be depicted in a particular configuration, compounds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned. When chiral centers are found in the derivatives of this invention, it is to be understood that this invention encompasses all possible stereoisomers. For example, in compounds according to formula **H**, the carbon atoms to which $-OR_9$ and $-CO_2R_1$ are attached may have an R,R or S,S or S,R or R,S configuration. Similarly, in formula **Q**, the carbon atoms to which R_2, R_5, R_{14}, $-OR_9$ and $-CH_2OR_{13}$ are attached may have an R,R,R,R or S,S,S,S or S,R,R,R or R,S,S,S or R,S,R,R or S,R,S,S or R,R,S,R or S,S,R,S or R,R,R,S or S,S,S,R or S,S,R,R or R,R,S,S or S,R,S,R or R,S,R,S or S,R,R,S or R,S,S,R configuration.

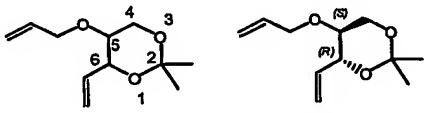
The terms "optically pure compound" or "optically pure isomer" refers to a single stereoisomer of a chiral compound regardless of the configuration of the said compound.

For purpose of this application, all sugars are referenced using conventional three-letter nomenclature. All sugars are assumed to be in the D-form unless otherwise noted, except for fucose, which is in the L-form. Further, all sugars are in the pyranose form.

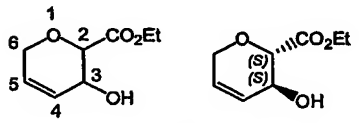
The following examples of nomenclature, numbering systems and stereochemical assignments are provided for reference.



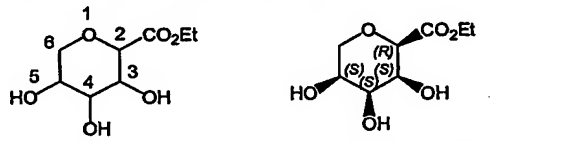
(2S,3R)-2-Allyloxy-pent-4-ene-1,3-diol



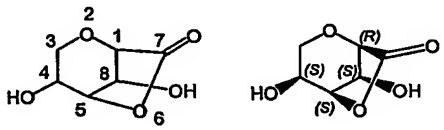
(5S,6R)-5-Allyloxy-2,2-dimethyl-4-vinyl-[1,3]dioxane



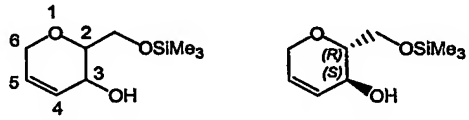
(2S,3S)- 3-Hydroxy-3,6-dihydro-2*H*-pyran-2-carboxylic acid ethyl ester



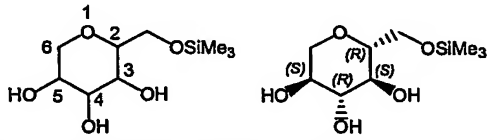
(2R,3S,4S,5S)-3,4,5-Trihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester



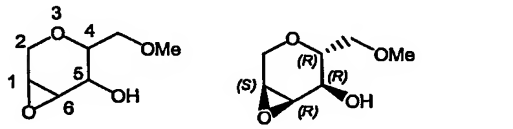
(1R,4S,5S,8S)-4,8-Dihydroxy-2,6-dioxa-bicyclo[3.2.1]octan-7-one



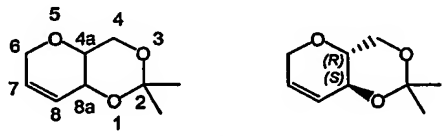
(2R,3S)-2-Trimethylsilanyloxymethyl-3,6-dihydro-2*H*-pyran-3-ol



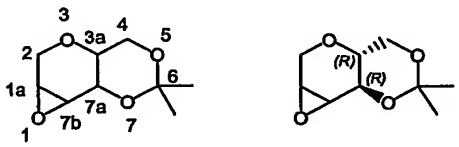
(2R,3S,4R,5S)-2-Trimethylsilanyloxymethyl-tetrahydro-pyran-3,4,5-triol



(1S,4R,5R,6R)-4-Methoxymethyl-3,7-dioxa-bicyclo[4.1.0]heptan-5-ol



(4aR,8aS)-2,2-Dimethyl-4,4a,6,8a-tetrahydro-pyrano[3,2-*d*][1,3]dioxine



(3aR,7aR)-6,6-Dimethyl-hexahydro-1,3,5,7-tetraoxa-cyclopropa[*a*]naphthalene

The term "substantially homogeneous" refers to collections of molecules wherein at least 80%, preferably at least about 90% and more preferably at least about 95% of the molecules are a single compound or a single stereoisomer thereof.

As used herein, the term "attached" signifies a stable covalent bond, certain preferred points of attachment being apparent to those skilled in the art.

The term "Lewis acid" refers to a molecule that can accept an unshared pair of electrons and as such would be obvious to one of ordinary skill and knowledge in the art. The definition of "Lewis acid" includes but is not limited to: boron trifluoride, boron trifluoride etherate, boron trifluoride tetrahydrofuran complex, boron trifluoride tert-butyl-methyl ether complex, boron trifluoride dibutyl ether complex, boron trifluoride dihydrate, boron trifluoride di-acetic acid complex, boron trifluoride dimethyl sulfide complex, boron trichloride, boron trichloride dimethyl sulfide complex, boron tribromide, boron tribromide dimethyl sulfide complex, boron triiodide, triimethoxyborane, triethoxyborane, trimethylaluminum, triethylaluminum, aluminum trichloride, aluminum trichloride tetrahydrofuran complex, aluminum tribromide, titanium tetrachloride, titanium tetrabromide, titanium iodide, titanium tetraethoxide, titanium tetraisopropoxide, scandium (III) trifluoromethanesulfonate, yttrium (III) trifluoromethanesulfonate, ytterbium (III) trifluoromethanesulfonate, lanthanum (III) trifluoromethanesulfonate, zinc (II) chloride, zinc (II) bromide, zinc (II) iodide, zinc (II) trifluoromethanesulfonate, zinc (II) sulfate, magnesium sulfate, lithium perchlorate, copper (II) trifluoromethanesulfonate, copper (II) tetrafluoroborate and the like. Certain Lewis acids may have optically pure ligands attached to the electron acceptor atom, as set forth in Corey, E. J. Angewandte Chemie, International Edition (2002), 41(10), 1650-1667; Aspinall, H. C. Chemical Reviews (Washington, DC, United States) (2002), 102(6), 1807-1850; Groger, H. Chemistry--A European Journal (2001), 7(24), 5246-5251; Davies, H. M. L. Chemtracts (2001), 14(11), 642-645; Wan, Y. Chemtracts (2001), 14(11), 610-615; Kim, Y. H. Accounts of Chemical Research (2001), 34(12), 955-962; Seebach, D. Angewandte Chemie, International Edition (2001), 40(1), 92-138; Blaser, H. U. Applied Catalysis, A: General (2001), 221(1-2), 119-143; Yet, L. Angewandte Chemie, International Edition (2001), 40(5), 875-877; Jorgensen, K. A. Angewandte Chemie, International Edition (2000), 39(20), 3558-3588; Dias, L. C. Current Organic Chemistry (2000), 4(3), 305-342; Spindler, F. Enantiomer (1999), 4(6), 557-568; Fodor, K. Enantiomer (1999), 4(6), 497-511; Shimizu, K. D.; Comprehensive Asymmetric Catalysis I-III (1999), 3, 1389-1399; Kagan, H. B. Comprehensive Asymmetric Catalysis I-III (1999), 1, 9-30; Mikami, K. Lewis Acid Reagents (1999), 93-136 and all references cited therein. Such Lewis acids maybe used by one of ordinary skill and knowledge in the art to produce optically pure compounds from achiral starting materials.

The term "acylating agent" refers to a molecule that can transfer an alkylcarbonyl, substituted alkylcarbonyl or aryl carbonyl group to another molecule. The definition of "acylating agent" includes but is not limited to ethyl acetate, vinyl acetate, vinyl propionate, vinyl butyrate, isopropenyl acetate, 1-ethoxyvinyl acetate, trichloroethyl butyrate, trifluoroethyl butyrate, trifluoroethyl laureate, S-ethyl thiooctanoate, biacetyl monooxime acetate, acetic anhydride, succinic anhydride, diketene, diallyl carbonate, carbonic acid but-3-enyl ester cyanomethyl ester, amino acid and the like.

The term "nucleophile" or "nucleophilic reagent" refers to a negatively charged or neutral molecule that has an unshared pair of electrons and as such would be obvious to one of ordinary skill and knowledge in the art. The definition of "nucleophile" includes but is not limited to: water, alkylhydroxy, alkoxy anion, arylhydroxy, aryloxy anion, alkylthiol, alkylthio anion, arylthiol, arylthio anion, ammonia, alkylamine, arylamine, alkylamine anion, arylamine anion, hydrazine, alkyl hydrazine, arylhydrazine, alkylcarbonyl hydrazine, arylcarbonyl hydrazine, hydrazine anion, alkyl hydrazine anion, arylhydrazine anion, alkylcarbonyl hydrazine anion, arylcarbonyl hydrazine anion, cyanide, azide, hydride, alkyl anion, aryl anion and the like.

The term "electrophile" or "electrophilic reagent" refers to a positively charged or neutral molecule that has an open valence shell and as such would be obvious to one of ordinary skill and knowledge in the art. The definition of "electrophile" includes but is not limited to: hydronium, acylium, lewis acids, such as for example, boron trifluoride and the like, halogens, such as for example Br_2 and the like, carbocations, such as for example tert-butyl cation and the like, diazomethane, trimethylsilyldiazomethane, alkyl halides, such as for example methyl iodide, benzyl bromide and the like, alkyl triflates, such as for example methyl triflate and the like, alkyl sulfonates, such as for example ethyl toluenesulfonate, butyl methanesulfonate and the like, acyl halides, such as for example acetyl chloride, benzoyl bromide and the like, acid anhydrides, such as for example acetic anhydride, succininc anhydride, maleic anhydride and the like, isocyanates, such as for example methyl isocyanate, phenylisocyanate and the like, chloroformates, such as for example methyl chloroformate, ethyl chloroformate, benzyl chloroformate and the like, sulfonyl halides, such as for example methanesulfonyl chloride, p-tolunesulfonyl chloride and the like, silyl halides, such as for example trimethylsilyl chloride, tertbutyldimethyl silyll chloride and the like, phosphoryl halide such as for example

dimethyl chlorophosphate and the like, alpha-beta-unsaturated carbonyl compounds such as for example acrolein, methyl vinyl ketone, cinnamaldehyde and the like.

The term "oxidant" refers to any reagent that will increase the oxidation state of a carbon atom in the starting material by either adding an oxygen atom to this carbon or removing an electron from this carbon and as such would be obvious to one of ordinary skill and knowledge in the art. The definition of "oxidant" includes but is not limited to: osmium tetroxide, ruthenium tetroxide, ruthenium trichloride, potassium permanganate, meta-chloroperbenzoic acid, hydrogen peroxide, dimethyl dioxirane and the like.

The term "metal ligand" refers to a molecule that has an unshared pair of electrons and can coordinate to a metal atom and as such would be obvious to one of ordinary skill and knowledge in the art. The definition of "metal ligand" includes but is not limited to: water, alkoxy anion, alkylthio anion, ammonia, trialkylamine, triarylamine, trialkylphosphine, triarylphosphine, cyanide, azide and the like.

The term "epoxidation reagent" refers to any reagent that will transform an alkene into an epoxide. The definition of "epoxidation reagent" includes but is not limited to: oxygen, tert-butyl hydroperoxide, meta-chloroperbenzoic acid, dimethyl dioxirane, oxone, sodium hypochlorite, sodium periodate, iodosylbenzene and the like. Certain transition metals and ligands facilitate the epoxidation of alkenes. Examples of such transition metal reagents include: titanium tetraisopropoxide, polymer supported cyclopentadienyl titanium trichloride, zirconium tetraethoxide, hafnium tetraisopropoxide, vanadium pentoxide, niobium pentaethoxide, tantalum pentaisopropoxide, manganese (II) trifluoromethanesulfonate, iron (III) acetylacetonate, molybdenum hexacarbonyl, ruthenium dichloride tris(triphenylphosphine), cobalt (II) trifluoromethanesulfonate, and the like. Examples of such ligands include: (R,R) diethyl tartarate, (S,S) diethyl tartarate, N-ethyl ephedrine, N-methylprolinol, porphyrin, 2,2'-[[(1S,2S)-1,2-diphenyl-1,2-ethanediyl]-bis(nitrilomethylidyne)]bis[6-(1,1-dimethylethyl)-4-methyl-phenol, 2,2'-[[(1R,2R)-1,2-diphenyl-1,2-ethanediyl]-bis(nitrilomethylidyne)]bis[6-(1,1-dimethylethyl)-4-methyl-phenol, 2,2'-[(1R,2R)-1,2-cyclohexanediylbis[(E)-nitrilomethylidyne]]bis[6-(1,1-dimethylethyl)-4-methyl-phenol and the like. Such chiral ligands maybe used by one of ordinary skill and knowledge in the art to produce optically pure epoxides from alkene starting materials.

The term "reducing reagent" refers to any reagent that will decrease the oxidation state of a carbon atom in the starting material by either adding a hydrogen atom to this carbon or adding an electron to this carbon and as such would be obvious to one of ordinary skill and knowledge in the art. The definiton of "reducing reagent" includes but is not limited to: borane-dimethyl sulfide complex, 9-borabicyclo[3.3.1.]nonane (9-BBN), catechol borane, lithium borohydride, sodium borohydride, sodium borohydride-methanol complex, potassium borohydride, sodium hydroxyborohydride, lithium triethylborohydride, lithium n-butylborohydride, sodium cyanoborohydride, calcium (II) borohydride, lithium aluminum hydride, diisobutylaluminum hydride, n-butyl-diisobutylaluminum hydride, sodium bis-methoxyethoxyaluminum hydride, triethoxysilane, diethoxymethylsilane, lithium hydride, lithium, sodium, hydrogen Ni/B, and the like. Certain acidic and Lewis acidic reagents enhance the activity of reducing reagents. Examples of such acidic reagents include: acetic acid, methanesulfonic acid, hydrochloric acid, and the like. Examples of such Lewis acidic reagents include: trimethoxyborane, triethoxyborane, aluminum trichloride, lithium chloride, vanadium trichloride, dicyclopentadienyl titanium dichloride, cesium fluoride, potassium fluoride, zinc (II) chloride, zinc (II) bromide, zinc (II) iodide, and the like.

The term "coupling reagent" refers to any reagent that will activate the carbonyl of a carboxylic acid and facilitate the formation of an ester or amide bond. The definition of "coupling reagent" includes but is not limited to: acetyl chloride, ethyl chloroformate, dicyclohexylcarbodiimide (DCC), diisopropyl carbodiiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI), N-hydroxybenzotriazole (HOBT), N-hydroxysuccinimide (HOSu), 4-nitrophenol, pentafluorophenol, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), O-benzotriazole-N,N,N'N'-tetramethyluronium hexafluorophosphate (HBTU), benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP), benzotriazole-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate, bromo-trispyrrolidino- phosphonium hexafluorophosphate, 2-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU), O-(N-succinimidyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TSTU), tetramethylfluoroformamidinium hexafluorophosphate and the like.

The terms "resin", "resin bound", "polymeric resin", "polymeric resin support", "polymeric support" or "solid support" refer to, at all occurrences, a bead or other solid

support, which would be obvious to one of ordinary skill and knowledge in the art. The preferred polymer resins for use herein are the Merrifield, hydroxymethyl, aminomethyl, benzhydrylamine, 4-methylbenhydrylamine, Wang and Rink resins and the like (available commercially from Advanced Chemtech, Chemimpex and the like). Other solid supports that are suitably substituted and made of a cross-linked polystyrene resin or polyethylene glycol-polystyrene resin can also be used. Additionally, a "linker", defined here as any aliphatic or aromatic reagent that tethers a given organic or organometallic compound to the solid-support and which lacks functionality that will participate in any synthetic chemistry subsequently carried out on the solid-support, can be used.

The term "removable protecting group" or "protecting group" refers to any group which when bound to a functionality, such as the oxygen atom of a hydroxyl or carboxyl group or the nitrogen atom of an amino group, prevents reactions from occurring at these functional groups and which protecting group can be removed by conventional chemical or enzymatic steps to reestablish the functional group. The particular removable protecting group employed is not critical.

The definition of "hydroxyl protecting group" includes but is not limited to:

a) Methyl, tert-butyl, allyl, propargyl, p-chlorophenyl, p-methoxyphenyl, p-nitrophenyl, 2,4-dinitrophenyl, 2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl, methoxymethyl, methylthiomethyl, (phenyldimethylsilyl)methoxymethyl, benzyloxymethyl, p-methoxy-benzyloxymethyl, p-nitrobenzyloxymethyl, o-nitrobenzyloxymethyl, (4-methoxyphenoxy)methyl, guaiacolmethyl, tert-butoxymethyl, 4-pentenyloxymethyl, tert-butyldimethylsiloxymethyl, thexyldimethylsiloxymethyl, tert-butyldiphenylsiloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl, menthoxymethyl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-[2-(trimethylsilyl)ethoxy]ethyl, 1-methyl-1-ethoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 1-methyl-1-phenoxyethyl, 2,2,2-trichloroethyl, 1-dianisyl-2,2,2-trichloroethyl, 1,1,1,3,3,3-hexafluoro-2-phenylisopropyl, 2-trimethylsilylethyl, 2-(benzylthio)ethyl, 2-(phenylselenyl)ethyl, tetrahydropyranyl, 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydropyranyl S,S-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1-(2-fluorophenyl)-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl and the like;

b) Benzyl, 2-nitrobenzyl, 2-trifluoromethylbenzyl, 4-methoxybenzyl, 4-nitrobenzyl, 4-chlorobenzyl, 4-bromobenzyl, 4-cyanobenzyl, 4-phenylbenzyl, 4-acylaminobenzyl, 4-azidobenzyl, 4-(methylsulfinyl)benzyl, 2,4-dimethoxybenzyl, 4-azido-3-chlorobenzyl, 3,4-dimethoxybenzyl, 2,6-dichlorobenzyl, 2,6-difluorobenzyl, 1-pyrenylmethyl, diphenylmethyl, 4,4'-dinitrobenzhydryl, 5-benzosuberyl, triphenylmethyl (Trityl), α-naphthyldiphenylmethyl, (4-Methoxyphenyl)-diphenyl-methyl, di-(p-methoxyphenyl)-phenylmethyl, tri-(p-methoxyphenyl)methyl, 4-(4'-bromophenacyloxy)-phenyldiphenylmethyl, 4,4',4"-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4"-tris(levulinoyloxyphenyl)methyl, 4,4'-dimethoxy-3"-[N-(imidazolylmethyl)]trityl, 4,4'-dimethoxy-3"-[N-(imidazolylethyl)carbamoyl]trityl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 4-(17-tetrabenzo[a,c,g,l]fluorenylmethyl)-4,4'-dimethoxytrityl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl and the like;

c) Trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, tribenzylsilyl, tri-p-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, di-tert-butylmethylsilyl, tris(trimethylsilyl)silyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, tert-butylmethoxyphenylsilyl, tert-butoxydiphenylsilyl and the like;

d) $-C(O)R^8$, where R^8 is selected from alkyl, substituted alkyl, aryl and more specifically R^8 = hydrogen, methyl, ethyl, tert-butyl, adamantyl, crotyl, chloromethyl, dichloromethyl, trichloromethyl, trifluoromethyl, methoxymethyl, triphenylmethoxymethyl, phenoxymethyl, 4-chlorophenoxymethyl, phenylmethyl, diphenylmethyl, 4-methoxycrotyl, 3-phenylpropyl, 4-pentenyl, 4-oxopentyl, 4,4-(ethylenedithio)pentyl, 5-[3-bis(4-methoxyphenyl)hydroxymethylphenoxy]- 4-oxopentyl, phenyl, 4-methylphenyl, 4-nitrophenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 4-phenylphenyl, 2,4,6-trimethylphenyl, α-naphthyl, benzoyl and the like;

e) $-C(O)OR^8$, where R^8 is selected from alkyl, substituted alkyl, aryl and more specifically R^8 = methyl, methoxymethyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloromethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 2-(trimethylsilyl)ethyl, 2-(phenylsulfonyl)ethyl, isobutyl, tert-Butyl, vinyl, allyl, 4-nitrophenyl, benzyl, 2-nitrobenzyl, 4-nitrobenzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 2-(methylthiomethoxy)ethyl, 2-dansenylethyl, 2-(4-nitrophenyl)ethyl, 2-(2,4-dinitrophenyl)ethyl, 2-cyano-1-phenylethyl, thiobenzyl, 4-ethoxy-1-naphthyl and the like.

The definition of "amino protecting group" includes but is not limited to:

a) 2-methylthioethyl, 2-methylsulfonylethyl, 2-(p-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethylthiophenyl, 2-phosphonioethyl, 1-methyl-1-(triphenylphosphonio)ethyl, 1,1-dimethyl-2-cyanoethyl, 2-dansylethyl, 2-(4-nitrophenyl)ethyl, 4-phenylacetoxybenzyl, 4-azidobenzyl, 4-azidomethoxybenzyl, m-chloro-p-acyloxybenzyl, p-(dihydroxyboryl)benzyl, 5-benzisoxazolylmethyl, 2-(trifluoromethyl)-6-chromonytmethyl, m-nitrophenyl, 3.5-dimethoxybenzyl, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl, o-nitrobenzyl, α-methylnitropiperonyl, 3,4-dimethoxy-6-nitrobenzyl, N-benzenesulfenyl, N-o-nitrobenzenesulfenyl, N-2,4-dinitrobenzenesulfenyl, N-pentachlorobenzenesulfenyl. N-2-nitro-4-methoxybenzenesulfenyl, N-triphenylmethylsulfenyl, N-1-(2,2,2-trifluoro-1,1-diphenyl)ethylsulfenyl, N-3-nitro-2-pyridinesulfenyl, N-p-toluenesulfonyl, N-benzenesulfonyl, N-2,3,6-trimethyl-4-methoxybenzenesulfonyl, N-2,4,6-trimethoxybenzene-sulfonyl, N-2,6-dimethyl-4-methoxybenzenesulfonyl, N-pentamethylbenzenesulfonyl, N-2,3,5.6-tetramethyl-4-methoxybenzenesulfonyl and the like;

b) $-C(O)OR^8$, where R^8 is selected from alkyl, substituted alkyl, aryl and more specifically R^8 = methyl, ethyl, 9-fluorenylmethyl, 9-(2-sulfo)fluorenylmethyl. 9-(2,7-dibromo)fluorenylmethyl, 17-tetrabenzo[a,c,g,i]fluorenylmethyl. 2-chloro-3-indenylmethyl, benz[f]inden-3-ylmethyl, 2,7-di-t-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl, 1,1-dioxobenzo[b]thiophene-2-ylmethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 2-chloroethyl, 1.1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenylyl)ethyl, 1-(3,5-di-tert-butylphenyl)-1-methylethyl, 2-(2'-pyridyl)ethyl, 2-(4'-pyridyl)ethyl, 2,2-bis(4'-nitrophenyl)ethyl, N-(2-pivaloylamino)-1,1-dimethylethyl, 2-[(2-nitrophenyl)dithio]-1-phenylethyl, tert-butyl, 1-adamantyl, 2-adamantyl, Vinyl, allyl, 1-Isopropylallyl, cinnamyl. 4-nitrocinnamyl, 3-(3'-pyridyl)prop-2-enyl, 8-quinolyl, N-Hydroxypiperidinyl, alkyldithio, benzyl, p-methoxybenzyl, p-nitrobenzyl, p-bromobenzyl. p-chlorobenzyl, 2,4-dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, diphenylmethyl, tert-amyl, S-benzyl thiocarbamate, butynyl, p-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, p-decyloxybenzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, o-(N,N'-dimethylcarboxamido)benzyl, 1,1-dimethyl-3-(N,N'-dimethylcarboxamido)propyl, 1,1-dimethylpropynyl, di(2-pyridyl)methyl, 2-furanylmethyl, 2-Iodoethyl, isobornyl, isobutyl, isonicotinyl, p-(p'-methoxyphenylazo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropylmethyl, 1-methyl-1-(p-phenylazophenyl)ethyl, 1 -methyl-1-phenylethyl, 1-

methyl-1-4'-pyridylethyl, phenyl, p-(phenylazo)benzyl, 2,4,6-tri-methylphenyl, 4-(trimethylammonium)benzyl, 2,4,6-trimethylbenzyl and the like.

The definition of "carboxyl protecting group" includes but is not limited to: 2-N-(morpholino)ethyl, choline, methyl, methoxyethyl, 9-Fluorenylmethyl, methoxymethyl, methylthiomethyl, tetrahydropyranyl, tetrahydrofuranyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, benzyloxymethyl, pivaloyloxymethyl, phenylacetoxymethyl, triisopropylsilylmethyl, cyanomethyl, acetol, p-bromophenacyl. α-methylphenacyl, p-methoxyphenacyl, desyl, carboxamidomethyl, p-azobenzenecarboxamido-methyl, N-phthalimidomethyl, (methoxyethoxy)ethyl, 2,2,2-trichloroethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 4-chlorobutyl, 5-chloropentyl, 2-(trimethylsilyl)ethyl, 2-methylthioethyl, 1,3-dithianyl-2-methyl, 2-(p-nitrophenylsulfenyl)ethyl, 2-(p-toluenesulfonyl)ethyl, 2-(2'-pyridyl)ethyl, 2-(p-methoxyphenyl)ethyl, 2-(diphenylphosphino)ethyl, 1-methyl-1-phenylethyl, 2-(4-acetyl-2-nitrophenyl)ethyl, 2-cyanoethyl, heptyl, tert-butyl, 3-methyl-3-pentyl, dicyclopropylmethyl, 2,4-dimethyl-3-pentyl, cyclopentyl, cyclohexyl, allyl, methallyl, 2-methylbut-3-en-2-yl, 3-methylbut-2-(prenyl), 3-buten-1-yl, 4-(trimethylsilyl)-2-buten-1-yl, cinnamyl, α-methylcinnamyl, propargyl, phenyl, 2,6-dimethylphenyl, 2,6-diisopropylphenyl, 2,6-di-tert-butyl-4-methylphenyl, 2,6-di-tert-butyl-4-methoxyphenyl, p-(methylthio)phenyl, pentafluorophenyl, benzyl, triphenylmethyl, diphenylmethyl, bis(o-nitrophenyl)methyl, 9-anthrylmethyl, 2-(9,10-dioxo)anthrylmethyl. 5-dibenzosuberyl, 1-pyrenylmethyl, 2-(trifluoromethyl)-6-chromonylmethyl, 2,4,6-trimethylbenzyl, p-bromobenzyl, o-nitrobenzyl, p-nitrobenzyl, p-methoxybenzyl, 2.6-dimethoxybenzyl, 4-(methylsulfinyl)benzyl, 4-Sulfobenzyl, 4-azidomethoxybenzyl, 4-{a/-[1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl]amino}benzyl, piperonyl, 4-picolyl, trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, isopropyldimethylsilyl, phenyldimethylsilyl, di-tert-butylmethylsilyl, triisopropylsilyl and the like.

The term "Amino acid" refers to any of the naturally occurring amino acids, as well as synthetic analogs and derivatives thereof. Alpha-Amino acids comprise a carbon atom to which is bonded an amino group, a carboxy group, a hydrogen atom, and a distinctive group referred to as a "side chain". The side chains of naturally occurring amino acids are well known in the art and include, for example, hydrogen (e.g., as in glycine), alkyl (e.g., as in alanine, valine, leucine, isoleucine, proline), substituted alkyl

(e.g., as in threonine, serine, methionine, cysteine, aspartic acid, asparagine, glutamic acid, glutamine, arginine, and lysine), arylalkyl (e.g., as in phenylalanine), substituted arylalkyl (e.g., as in tyrosine), heteroarylalkyl (e.g., as in tryptophan, histidine) and the like. One of skill in the art will appreciate that the term "amino acid" can also include beta-, gamma-, delta-, omega- amino acids, and the like. Unnatural amino acids are also known in the art, as set forth in, Natchus, M. G. Organic Synthesis: Theory and Applications (2001), 5, 89-196; Ager, D. J. Current Opinion in Drug Discovery & Development (2001), 4(6), 800; Reginato, G. Recent Research Developments in Organic Chemistry (2000), 4(Pt. 1), 351-359; Dougherty, D. A. Current Opinion in Chemical Biology (2000), 4(6), 645-652; Lesley, S. A. Drugs and the Pharmaceutical Sciences (2000), 101(Peptide and Protein Drug Analysis), 191-205; Pojitkov, A. E. Journal of Molecular Catalysis B: Enzymatic (2000), 10(1-3), 47-55; Ager, D. J. Speciality Chemicals (1999), 19(1), 10-12, and all references cited therein. Stereoisomers (e.g., D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as alpha, alpha-disubstituted amino acids and other unconventional amino acids may also be suitable components for compounds of the present invention. Examples of unconventional amino acids include: 4-hydroxyproline, 3-methylhistidine, 5-hydroxylysine, and other similar amino acids and imino acids (e.g., 4-hydroxyproline).

The term "N-protected amino acid" refers to any amino acid which has a protecting group bound to the nitrogen of the amino functionality. This protecting group prevents reactions from occurring at the amino functional group and can be removed by conventional chemical or enzymatic steps to reestablish the amino functional group. The particular protecting group employed is not critical.

The term "O-protected amino acid" refers to any amino acid which has a protecting group bound to the oxygen of the carboxyl functionality. This protecting group prevents reactions from occurring at the carboxyl functional group and can be removed by conventional chemical or enzymatic steps to reestablish the carboxyl functional group. The particular protecting group employed is not critical.

The term "ring-closing metathesis catalyst" refers to an organometallic compound that catalyzes the formation of a cyclic molecule from an acyclic precursor in a single synthetic step. The definition of "ring-closing metathesis catalyst" includes but is not limited to: 2,6-diisopropylphenylimidoneophylidene molybdenum (IV) bis-(tert-butoxide),

2,6-diisopropylphenylimidoneophylidene molybdenum (IV) bis-(hexafluoro-tert-butoxide), 2,6-diisopropylphenylimidoneophylidene[racemic-BIPHEN] molybdenum (IV), 2,6-diisopropylphenylimidoneophylidene[(R)-(+)-BIPHEN] molybdenum (IV), 2,6-diisopropylphenylimidoneophylidene[(S)-(-)-BIPHEN] molybdenum (IV), bis-(tricyclohexylphosphine)benzylidine ruthenium (IV) dichloride, bis-(tricyclohexylphosphine)-3-methyl-2-butenylidene ruthenium (IV) dichloride, bis-(tricyclopentylphosphine)benzylidine ruthenium (IV) dichloride, bis-(tricyclopentylphosphine)-3-methyl-2-butenylidene ruthenium (IV) dichloride, tricyclohexylphosphine-(1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene)-benzylidine ruthenium (IV) dichloride, tricyclohexylphosphine-(1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene)-benzylidine ruthenium (IV) dichloride, (1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene)-2-isopropoxyphenylmethylene ruthenium (IV) dichloride, (tricyclopentylphosphine)-2-isopropoxyphenylmethylene ruthenium (IV) dichloride, (tricyclopentylphosphine)-2-methoxy-3-naphthylmethylene ruthenium (IV) dichloride, and the like. Such ring-closing metathesis catalysts maybe used by one of ordinary skill and knowledge in the art to produce optically pure compounds from achiral starting materials.

The term "resolving enzyme" refers to a lipase, esterase, peptidase, acylase or protease enzyme of mammalian, plant, fungal or bacterial origin. The source of the "resolving enzyme" includes human pancreas, pig pancreas, pig kidney, pig liver, rabbit liver, wheat germ, *Achromobacter sp., Alcaligenes sp., Aspergillus niger, Aspergillus oryzae, Bacillus licheniformis, Bacillus sp., Bacillus thermocatenulatus, Candida antartica type A, Candida antartica type B, Candida lipolytica, Candida rugosa* (or *Candida cylindracea*), *E. coli, Geotrichum candidum, Humicola sp., Mucor javanicus* (or *Rhizomucor javanicus*), *Mucor miehei* (or *Rhizomucor miehei*), *Penicillium camembertii* (or *Penicillium cyclopium*), *Penicillium roquefortii, Penicillium sp., Pseudomonas cepacia* (or *Burkholderia cepacia*), *Pseudomonas fluorescens, Pseudomonas fragi, Pseudomonas glumae* (or *Chromobacterium viscosum*), *Pseudomonas sp., Pseudomonas stutzeri, Rhizopus delemar, Rhizopus javanicus, Rhizopus niveus, Rhizopus oryzae, Thermomyces lanuginose* (or *Humicola lanuginose*) and the like.

The definition of "resolving enzyme" includes but is not limited to:

1. Amano Lipase A (from *Aspergillus niger*), Amano Lipase M (from *Mucor javanicus*), Amano Lipase F (from *Rhizopus oryzae*), Amano Lipase G (from *Penicillium camembertii*), Amano Lipase R (from *Penicillium roquefortii),* Amano Newlase F (from

Rhizopus niveus), Amano lipase AY (from *Candida rugosa)*, Amano lipase PS (from *Pseudomonas cepacia)*, Amano Lipase AK (from *Pseudomonas fluorescens)*, Amano lipase CHE (from *Pseudomonas sp.)*, Amano Lipase PPL (from pig pancreas), Amano Lipase D (from *Rhizopus delemar*), Amano Lipase L (from *Candida lipolytica*), Amano Lipase AH (from *Pseudomonas cepacia*), Lipase Amano lipase PS-D (immobilized lipase from *Pseudomonas cepacia*), Amano Lipase PS-C (immobilized lipase from *Pseudomonas cepacia*) and the like.

2. Roche (cholesterol esterase, lyophilizate, from *Candida Rugosa)*, Roche (cholesterol esterase, sodium chloride solution, from *Candida Rugosa)*, Roche (esterase, suspension, from pig liver*)*, Roche Chirazyme E-1 (esterase, lyophilizate, from pig liver, fraction 1*)*, Roche Chirazyme E-1 (esterase, carrier-fixed, lyophilizate, from pig liver, fraction 1*)*, Roche Chirazyme E-2 (esterase, lyophilizate, from pig liver, fraction 2*)*, Roche Chirazyme L-1 (lipase, from *Bacillus thermocatenulatus*), Roche Chirazyme L-2 (lipase, solution, from *Candida antartica, type B*), Roche Chirazyme L-2 (lipase, lyophilizate, from *Candida antartica, type B)*, Roche Chirazyme L-2 (lipase, carrier-fixed, carrier 1, lyophilizate, from *Candida antartica, type B)*, Roche Chirazyme L-2 (lipase, carrier-fixed, carrier 2, lyophilizate, from *Candida antartica, type B)*, Roche Chirazyme L-2 (lipase, carrier-fixed, carrier 3, lyophilizate, from *Candida antartica, type B)*, Roche Chirazyme L-3 (lipase, lyophilizate, from *Candida Rugosa)*, Roche Chirazyme L-3 (purified lipase, lyophilizate, from *Candida Rugosa*), Roche Chirazyme L-3 (purified lipase, carrier-fixed, carrier 2, lyophilizate, from *Candida rugosa*), Roche Chirazyme L-5 (lipase, solution, from *Candida antartica, type A)*, Roche Chirazyme L-5 (lipase, lyophilizate, from *Candida antartica, type A*), Roche Chirazyme L-5 (lipase, carrier-fixed, carrier 1, lyophilizate, from *Candida antartica, type A)*, Roche Chirazyme L-6 (lipase, lyophilizate, from *Pseudomonas sp.*), Roche Chirazyme L-7 (lipase, lyophilizate, from porcine pancreas), Roche Chirazyme L-8 (lipase, solution, from *Thermomyces lanuginosus*), Roche Chirazyme L-8 (lipase, lyophilizate, from *Thermomyces lanuginosus*), Roche Chirazyme L-9 (lipase, solution, from *Mucor miehei*), Roche Chirazyme L-9 (lipase, lyophilizate, from *Mucor miehei*), Roche Chirazyme L-9 (lipase, carrier-fixed, carrier 1, dry, from *Mucor miehei*), Roche Chirazyme L-9 (lipase, carrier-fixed, carrier 2, lyophilizate, from *Mucor miehei*), Roche Chirazyme L-10 (lipase, lyophilizate, from *Alcaligenes sp.*), Roche (lipase, from pig pancreas) and the like.

3. Altus Biologics 1 (esterase from pig liver), Altus Biologics 2 (lipase from *Pseudomonas cepacia*), Altus Biologics 3 (lipase from pig pancreas), Altus Biologics 4 (lipase from *Candida rugosa*), Altus Biologics 5 (α-chymotrypsin), Altus Biologics 5

(penicillin acylase), Altus Biologics 7 (lipase from *Aspergillus niger*), Altus Biologics 8 (lipase from *Mucor miehei*), Altus Biologics 9 (ChiroCLEC™-CR, slurry, lipase from *Candida rugosa*), Altus Biologics 10 (Subtilisin Carlsberg), Altus Biologics 11 (lipase from *Candida antartica type A*), Altus Biologics 12 (lipase from *Candida lipolytica*), Altus Biologics 13 (lipase from *Candida antartica type B*), Altus Biologics 14 (lipase from *Humicola lanuginosa*), Altus Biologics 15 (protease from *Bacillus species*), Altus Biologics 16 (ChiroCLEC™-BL, slurry, peptidase from *Bacillus licheniformis*), Altus Biologics 17 (ChiroCLEC™-CR, dry, lipase from *Candida rugosa*), Altus Biologics 18 (ChiroCLEC™-BL, dry, peptidase from *Bacillus licheniformis*), Altus Biologics 19 (ChiroCLEC™-PC, slurry, lipase from *Pseudomonas cepacia*), Altus Biologics 20 (ChiroCLEC™-PC, dry, lipase from *Pseudomonas cepacia*), Altus Biologics 21 (ChiroCLEC™-EC, slurry, lipase from *E. coli*), Altus Biologics 22 (ChiroCLEC™-EC, dry, lipase from *E. coli*), Altus Biologics 23 (lipase from *Rhizopus delemar*), Altus Biologics 24 (lipase from *Rhizopus niveus*), Altus Biologics 25 (lipase from *Rhizopus oryzae*), Altus Biologics 26 (lipase from *Pseudomonas glumae*), Altus Biologics 27 (lipase from *Alcaligenes sp.*), Altus Biologics 28 (lipase from *Geotrichum candidum*), Altus Biologics 29 (lipase from *Mucor javanicus*), Altus Biologics 30 (protease from *Aspergillus oryzae*), Altus Biologics 31 (esterase from *Candida rugosa*), Altus Biologics 41 (protease from *Aspergillus niger*), Altus Biologics 42 (protease from *Aspergillus oryzae*), Altus Biologics 43 (protease from *Penicillium sp.*), Altus Biologics 45 (protease from *Aspergillus sp.*), Altus Biologics 51, Altus Biologics 52, Altus Biologics 54, Altus Biologics 55.

4. Sigma acylase (from pig kidney), Sigma esterase (solution from pig liver), Sigma esterase (from pig liver), Sigma esterase (from rabbit liver), Sigma lipase (from human pancreas), Sigma lipase (from pig pancreas), Sigma lipase (from wheat germ), Sigma lipase (from *Candida rugosa*), Sigma lipase (from *Mucor javanicus*), Sigma lipase (from *Mucor miehei*), Sigma lipase (from *Pseudomonas cepacia*), Sigma lipase (from *Rhizopus niveus*), Sigma lipase (immobilized on cellulose from *Pseudomonas sp.*), Sigma lipase (from *Candida rugosa*), Sigma lipase (from *Rhizopus arrhizus*), Sigma lipase (from *Chromobacterium viscosum*), Sigma lipase (from *Pseudomonas sp.*) and the like.

5. Novozym 435 (lipase from *Candida antarctica*), Novozym™ CALB L (lipase from *Candida* Antarctica), Lecitase Novo™ (esterase from *Aspergillus oryzae*), Lecitase Ultra™ (esterase from *Thermomyces lanuginosus*), Lipozyme™ RM IM (lipase from *Rhizomucor miehei*), Lipozyme™ TL 100 L (lipase from *Thermomyces lanuginosus*), Lipozyme™ TL IM (lipase from *Thermomyces* lanuginosus) and the like.

6. Meito Sangyo Lipase MY (from *Candida cylindracea*), Meito Sangyo Lipase OF (from *Candida cylindracea*), Meito Sangyo Lipase AL (from *Achromobacter sp.*), Meito Sangyo Lipase ALC/ALG (from *Achromobacter sp.*), Meito Sangyo Lipase PL (from *Alcaligenes sp.*), Meito Sangyo Lipase PLC/PLG (from *Alcaligenes sp.*), Meito Sangyo Lipase QLM (from *Alcaligenes sp.*), Meito Sangyo Lipase QLC/QLG (from *Alcaligenes sp.*), Meito Sangyo Lipase SL (from *Burkholderia cepacia*), Meito Sangyo Lipase TL (from *Pseudomonas stutzeri*), Meito Sangyo Lipase UL (from *Rhizopus sp.*) and the like

The term "Prodrug" refers to an agent that is converted into the parent drug in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A prodrug may be converted into the parent drug by various mechanisms, including enzymatic processes and metabolic hydrolysis. See Harper, "Drug Latentiation" in Jucker, ed. Progress in Drug Research 4:221-294 (1962); Morozowich et al., "Application of Physical Organic Principles to Prodrug Design" in E. B. Roche ed. Design of Biopharmaceutical Properties through Prodrugs and Analogs, APHA Acad. Pharm. Sci. (1977); Bioreversible Carriers in Drug in Drug Design, Theory and Application, E. B. Roche, ed., APHA Acad. Pharm. Sci. (1987); Design of Prodrugs, H. Bundgaard, Elsevier (1985); Wang et al. "Prodrug approaches to the improved delivery of peptide drug" in Curr. Pharm. Design. 5(4):265-287 (1999); Pauletti et al. (1997) Improvement in peptide bioavailability: Peptidomimetics and Prodrug Strategies, Adv. Drug. Delivery Rev. 27:235-256; Mizen et al. (1998) "The Use of Esters as Prodrugs for Oral Delivery of .beta.-Lactam antibiotics," Pharm. Biotech. 11,:345-365; Gaignault et al. (1996) "Designing Prodrugs and Bioprecursors I. Carrier Prodrugs," Pract. Med. Chem. 671-696; Asghamejad, "Improving Oral Drug Transport", in Transport Processes in Pharmaceutical Systems, G. L. Amidon, P. I. Lee and E. M. Topp, Eds., Marcell Dekker, p. 185-218 (2000); Balant et al., "Prodrugs for the improvement of drug absorption via different routes of administration", Eur. J. Drug Metab. Pharmacokinet., 15(2): 143-53 (1990); Balimane and Sinko, "Involvement of multiple transporters in the oral absorption of nucleoside analogues", Adv. Drug Delivery Rev., 39(1-3): 183-209 (1999); Browne, "Fosphenytoin (Cerebyx)", Clin. Neuropharmacol. 20(1): 1-12 (1997); Bundgaard, "Bioreversible derivatization of drugs--principle and applicability to improve the therapeutic effects of drugs", Arch. Pharm.

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The terms "halogen", "halide" or "halo" include fluorine, chlorine, bromine, and iodine.

The terms "alkyl" and "substituted alkyl" are interchangeable and include substituted and unsubstituted C_1-C_{10} straight chain saturated aliphatic hydrocarbon groups, substituted and unsubstituted C_2-C_{10} straight chain unsaturated aliphatic

hydrocarbon groups, substituted and unsubstituted C_4-C_{10} branched saturated aliphatic hydrocarbon groups, substituted and unsubstituted C_4-C_{10} branched unsaturated aliphatic hydrocarbon groups, substituted and unsubstituted C_3-C_8 cyclic saturated aliphatic hydrocarbon groups, substituted and unsubstituted C_5-C_8 cyclic unsaturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, the definition of "alkyl" shall include but is not limited to: methyl (Me), ethyl (Et), propyl (Pr), butyl (Bu), pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, ethenyl, propenyl, butenyl, penentyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, isopropyl (i-Pr), isobutyl (i-Bu), *tert*-butyl (*t*-Bu), *sec*-butyl (*s*-Bu), isopentyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, methylcyclopropyl, ethylcyclohexenyl, butenylcyclopentyl, adamantyl, norbornyl and the like. Alkyl substituents are independently selected from the group comprising halogen, -OH, -SH, $-NH_2$, -CN, $-NO_2$, =O, $=CH_2$, trihalomethyl, carbamoyl, arylC_{0-10}alkyl, heteroarylC_{0-10}alkyl, C_{1-10}alkyloxy, arylC_{0-10}alkyloxy, C_{1-10}alkylthio, arylC_{0-10}alkylthio, C_{1-10}alkylamino, arylC_{0-10}alkylamino, N-aryl-N-C_{0-10}alkylamino, C_{1-10}alkylcarbonyl, arylC_{0-10}alkylcarbonyl, C_{1-10}alkylcarboxy, arylC_{0-10}alkylcarboxy, C_{1-10}alkylcarbonylamino, arylC_{0-10}alkylcarbonylamino, tetrahydrofuryl, morpholinyl, piperazinyl, hydroxypyronyl, $-C_{0-10}$alkylCOOR$_{21}$ and $-C_{0-10}$alkylCONR$_{22}$R$_{23}$ wherein R_{21}, R_{22} and R_{23} are independently selected from hydrogen, alkyl, aryl, or R_{22} and R_{23} are taken together with the nitrogen to which they are attached forming a saturated cyclic or unsaturated cyclic system containing 3 to 8 carbon atoms with at least one substituent as defined herein.

The term "alkyloxy" (e.g. methoxy, ethoxy, propyloxy, allyloxy, cyclohexyloxy) represents an alkyl or substituted alkyl group as defined above having the indicated number of carbon atoms attached through an oxygen bridge. The term "alkyloxyalkyl" represents an alkyloxy group attached through an alkyl or substituted alkyl group as defined above having the indicated number of carbon atoms.

The term "alkylthio" (e.g. methylthio, ethylthio, propylthio, cyclohexenylthio and the like) represents an alkyl or substituted alkyl group as defined above having the indicated number of carbon atoms attached through a sulfur bridge. The term "alkylthioalkyl" represents an alkylthio group attached through an alkyl or substituted alkyl group as defined above having the indicated number of carbon atoms.

The term "alkylamino" (e.g. methylamino, diethylamino, butylamino, N-propyl-N-hexylamino, (2-cyclopentyl)propylamino, hexenylamino, and the like) represents one or two alkyl or substituted alkyl groups as defined above having the indicated number of carbon atoms attached through an amine bridge. The alkyl or substituted alkyl groups maybe taken together with the nitrogen to which they are attached forming a cyclic system containing 3 to 10 carbon atoms with at least one substituent as defined above. The term "alkylaminoalkyl" represents an alkylamino group attached through an alkyl or substituted alkyl group as defined above having the indicated number of carbon atoms.

The term "alkylhydrazino" (e.g. methylhydrazino, ethylhydrazino, butylhydrazino, (2-cyclopentyl)propylhydrazino, cyclohexanehydrazino, and the like) represents one alkyl or substituted alkyl group as defined above having the indicated number of carbon atoms attached through a hydrazine bridge. The term "alkylhydrazinoalkyl" represents an alkylhydrazino group attached through an alkyl or substituted alkyl group as defined above having the indicated number of carbon atoms.

The term "alkylcarbonyl" (e.g. cyclooctylcarbonyl, pentylcarbonyl, 3-hexenylcarbonyl and the like) represents an alkyl or substituted alkyl group as defined above having the indicated number of carbon atoms attached through a carbonyl group. The term "alkylcarbonylalkyl" represents an alkylcarbonyl group attached through an alkyl or substituted alkyl group as defined above having the indicated number of carbon atoms.

The term "alkylcarboxy" (e.g. heptylcarboxy, cyclopropylcarboxy, 3-pentenylcarboxy and the like) represents an alkylcarbonyl group as defined above wherein the carbonyl is in turn attached through an oxygen. The term "alkylcarboxyalkyl" represents an alkylcarboxy group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "alkylcarbonylamino" (e.g. hexylcarbonylamino, cyclopentylcarbonyl-aminomethyl, methylcarbonylaminophenyl and the like) represents an alkylcarbonyl group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of an amino group. The nitrogen group may itself be substituted with an alkyl or aryl group. The term "alkylcarbonylaminoalkyl" represents an alkylcarbonylamino group

attached through an alkyl group as defined above having the indicated number of carbon atoms. The nitrogen group may itself be substituted with an alkyl or aryl group.

The term "alkylcarbonylhydrazino" (e.g. ethylcarbonylhydrazino, tert-butylcarbonylhydrazino and the like) represents an alkylcarbonyl group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of a hydrazino group.

The term "aryl" represents an unsubstituted, mono-, di- or trisubstituted monocyclic, polycyclic, biaryl aromatic groups covalently attached at any ring position capable of forming a stable covalent bond, certain preferred points of attachment being apparent to those skilled in the art (e.g., 3-phenyl, 4-naphtyl and the like). The aryl substituents are independently selected from the group consisting of halo, -OH, -SH, -CN, -NO_2, trihalomethyl, hydroxypyronyl, C_{1-10}alkyl, arylC_{0-10}alkyl, C_{0-10}alkyloxyC_{0-10}alkyl, arylC_{0-10}alkyloxyC_{0-10}alkyl, C_{0-10}alkylthioC_{0-10}alkyl, arylC_{0-10}alkylthioC_{0-10}alkyl, C_{0-10}alkylaminoC_{0-10}alkyl, arylC_{0-10}alkylaminoC_{0-10}alkyl, N-aryl-N-C_{0-10}alkylaminoC_{0-10}alkyl, C_{1-10}alkylcarbonylC_{0-10}alkyl, arylC_{0-10}alkylcarbonylC_{0-10}alkyl, C_{1-10}alkylcarboxyC_{0-10}alkyl, arylC_{0-10}alkylcarboxyC_{0-10}alkyl, C_{1-10}alkylcarbonylaminoC_{0-10}alkyl, arylC_{0-10}alkylcarbonylaminoC_{0-10}alkyl, –C_{0-10}alkylCOOR_{21}, and –C_{0-10}alkylCONR$_{22}$R$_{23}$ wherein R_{21}, R_{22} and R_{23} are independently selected from hydrogen, C_1-C_{10}alkyl, arylC_0-C_{10}alkyl, or R_{22} and R_{23} are taken together with the nitrogen to which they are attached forming a cyclic system containing 3 to 8 carbon atoms with at least one substituent as defined above.

The definition of "aryl" includes but is not limited to phenyl, biphenyl, naphthyl, dihydronaphthyl, tetrahydronaphthyl, indenyl, indanyl, azulenyl, anthryl, phenanthryl, fluorenyl, pyrenyl and the like.

The term "arylalkyl" (e.g. (4-hydroxyphenyl)ethyl, (2-aminonaphthyl)hexenyl and the like) represents an aryl group as defined above attached through an alkyl or substituted alkyl group as defined above having the indicated number of carbon atoms.

The term "arylcarbonyl" (e.g. 2-thiophenylcarbonyl, 3-methoxyanthrylcarbonyl and the like) represents an aryl group as defined above attached through a carbonyl group.

The term "arylalkylcarbonyl" (e.g. (2,3-dimethoxyphenyl)propylcarbonyl, (2-chloronaphthyl)pentenyl-carbonyl, imidazolylcyclopentylcarbonyl and the like) represents an arylalkyl group as defined above wherein the alkyl group is in turn attached through a carbonyl.

The term "aryloxy" (e.g. phenoxy, naphthoxy, 3-methylphenoxy, and the like) represents an aryl or substituted aryl group as defined above having the indicated number of carbon atoms attached through an oxygen bridge. The term "aryloxyalkyl" represents an aryloxy group attached through an alkyl or substituted alkyl group as defined above having the indicated number of carbon atoms.

The term "arylthio" (e.g. phenylthio, naphthylthio, 3-bromophenylthio, and the like) represents an aryl or substituted aryl group as defined above having the indicated number of carbon atoms attached through a sulfur bridge. The term "arylthioalkyl" represents an arylthio group attached through an alkyl or substituted alkyl group as defined above having the indicated number of carbon atoms.

The term "arylamino" (e.g. phenylamino, diphenylamino, naphthylamino, N-phenyl-N-naphthylamino, o-methylphenylamino, p-methoxyphenylamino, and the like) represents one or two aryl groups as defined above having the indicated number of carbon atoms attached through an amine bridge. The term "arylaminoalkyl" represents an arylamino group attached through an alkyl group as defined above having the indicated number of carbon atoms. The term "arylalkylamine" represents an aryl group attached through an alkylamino group as defined above having the indicated number of carbon atoms. The term "N-aryl-N-alkylamino" (e.g. N-phenyl-N-methylamino, N-naphthyl-N-butylamino, and the like) represents one aryl and one alkyl or substituted alkyl group as defined above having the indicated number of carbon atoms independently attached through an amine bridge.

The term "arylhydrazino" (e.g. phenylhydrazino, naphthylhydrazino, p-methoxyphenylhydrazino, and the like) represents one aryl or substituted aryl group as defined above having the indicated number of carbon atoms attached through a hydrazine bridge. The term "arylhydrazinoalkyl" represents an arylhydrazino group attached through an alkyl or substituted alkyl group as defined above having the indicated number of carbon atoms.

The term "arylcarbonylamino" (e.g. phenylcarbonylamino, naphthylcarbonylamino and the like) represents an arylcarbonyl group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of an amino group. The nitrogen group may itself be substituted with an alkyl or aryl group. The term "arylcarbonylaminoalkyl" represents an arylcarbonylamino group attached through an alkyl group as defined above having the indicated number of carbon atoms. The nitrogen group may itself be substituted with an alkyl or aryl group.

The term "arylcarbonylhydrazino" (e.g. phenylcarbonylhydrazino, naphthylcarbonylhydrazino and the like) represents an arylcarbonyl group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of a hydrazino group.

The terms "heteroaryl", "heterocycle" or "heterocyclic" refers to a monovalent unsaturated group having a single ring or multiple condensed rings, from 1 to 8 carbon atoms and from 1 to 4 hetero atoms selected from nitrogen, sulfur or oxygen within the ring. For the purposes of this application, the terms "heteroaryl", "heterocycle" or "heterocyclic" do not include carbohydrate rings (i.e. mono- or oligosaccharides).

Unless otherwise constrained by the definition for the "heteroaryl" substituent, such heterocyclic groups can be optionally substituted with 1 to 3 substituents selected from the group comprising: halo, -OH, -SH, -CN, -NO_2, trihalomethyl, hydroxypyronyl, C_{1-10}alkyl, arylC_{0-10}alkyl, C_{0-10}alkyloxyC_{0-10}alkyl, arylC_{0-10}alkyloxyC_{0-10}alkyl, C_{0-10}alkylthioC_{0-10}alkyl, arylC_{0-10}alkylthioC_{0-10}alkyl, C_{0-10}alkylaminoC_{0-10}alkyl, arylC_{0-10}alkylaminoC_{0-10}alkyl, N-aryl-N-C_{0-10}alkylaminoC_{0-10}alkyl, C_{1-10}alkylcarbonylC_{0-10}alkyl, arylC_{0-10}alkylcarbonylC_{0-10}alkyl, C_{1-10}alkylcarboxyC_{0-10}alkyl, arylC_{0-10}alkylcarboxyC_{0-10}alkyl, C_{1-10}alkylcarbonylaminoC_{0-10}alkyl, arylC_{0-10}alkylcarbonylaminoC_{0-10}alkyl, –C_{0-10}alkylCOOR_{21}, and –C_{0-10}alkylCONR$_{22}$R$_{23}$ wherein R_{21}, R_{22} and R_{23} are independently selected from hydrogen, C_1-C_{10}alkyl, arylC_0-C_{10}alkyl, or R_{22} and R_{23} are taken together with the nitrogen to which they are attached forming a cyclic system containing 3 to 8 carbon atoms with at least one substituent as defined above.

The definition of "heteroaryl" includes but is not limited to thienyl, benzothienyl, isobenzothienyl, 2,3-dihydrobenzothienyl, furyl, pyranyl, benzofuranyl, isobenzofuranyl,

2,3-dihydrobenzofuranyl, pyrrolyl, pyrrolyl-2,5-dione, 3-pyrrolinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, indolizinyl, indazolyl, phthalimidyl (or isoindoly-1,3-dione), imidazolyl, 2H-imidazolinyl, benzimidazolyl, pyridyl, pyrazinyl, pyradazinyl, pyrimidinyl, triazinyl, quinolyl, isoquinolyl, 4H-quinolizinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromanyl, benzodioxolyl, piperonyl, purinyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, benzthiazolyl, oxazolyl, isoxazolyl, benzoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolidinyl-2,5-dione, imidazolidinyl-2,4-dione, 2-thioxo-imidazolidinyl-4-one, imidazolidinyl-2,4-dithione, thiazolidinyl-2,4-dione, 4-thioxo-thiazolidinyl-2-one, piperazinyl-2,5-dione, tetrahydro-pyridazinyl-3,6-dione, 1,2-dihydro-[1,2,4,5]tetrazinyl-3,6-dione, [1,2,4,5]tetrazinanyl-3,6-dione, dihydro-pyrimidinyl-2,4-dione, pyrimidinyl-2,4,6-trione, 1H-pyrimidinyl-2,4-dione, 5-iodo-1H-pyrimidinyl-2,4-dione, 5-chloro-1H-pyrimidinyl-2,4-dione, 5-methyl-1H-pyrimidinyl-2,4-dione, 5-isopropyl-1H-pyrimidinyl-2,4-dione, 5-propynyl-1H-pyrimidinyl-2,4-dione, 5-trifluoromethyl-1H-pyrimidinyl-2,4-dione, 6-amino-9H-purinyl, 2-amino-9H-purinyl, 4-amino-1H-pyrimidinyl-2-one, 4-amino-5-fluoro-1H-pyrimidinyl-2-one, 4-amino-5-methyl-1H-pyrimidinyl-2-one, 2-amino-1,9-dihydro-purinyl-6-one, 1,9-dihydro-purinyl-6-one, 1H-[1,2,4]triazolyl-3-carboxylic acid amide, 2,6-diamino-N_6-cyclopropyl-9H-purinyl, 2-amino-6-(4-methoxyphenylsulfanyl)-9H-purinyl, 5,6-dichloro-1H-benzoimidazolyl, 2-isopropylamino-5,6-dichloro-1H-benzoimidazolyl, 2-bromo-5,6-dichloro-1H-benzoimidazolyl, and the like.

The term "saturated heterocyclic" represents an unsubstituted, mono-, di- or trisubstituted monocyclic, polycyclic saturated heterocyclic group covalently attached at any ring position capable of forming a stable covalent bond, certain preferred points of attachment being apparent to those skilled in the art (e.g., 1-piperidinyl, 4-piperazinyl and the like).

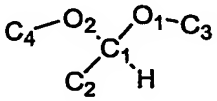
The saturated heterocyclic substituents are independently selected from the group consisting of halo, -OH, -SH, -CN, -NO_2, trihalomethyl, hydroxypyronyl, C_{1-10}alkyl, arylC_{0-10}alkyl, C_{0-10}alkyloxyC_{0-10}alkyl, arylC_{0-10}alkyloxyC_{0-10}alkyl, C_{0-10}alkylthioC_{0-10}alkyl, arylC_{0-10}alkylthioC_{0-10}alkyl, C_{0-10}alkylaminoC_{0-10}alkyl, arylC_{0-10}alkylaminoC_{0-10}alkyl, N-aryl-N-C_{0-10}alkylaminoC_{0-10}alkyl, C_{1-10}alkylcarbonylC_{0-10}alkyl, arylC_{0-10}alkylcarbonylC_{0-10}alkyl, C_{1-10}alkylcarboxyC_{0-10}alkyl, arylC_{0-10}alkylcarboxyC_{0-10}alkyl, C_{1-10}alkylcarbonylaminoC_{0-10}alkyl, arylC_{0-10}alkylcarbonylaminoC_{0-10}alkyl, –C_{0-10}alkylCOOR_{21}, and –C_{0-10}alkylCONR$_{22}$R$_{23}$ wherein R_{21}, R_{22} and R_{23} are independently selected from hydrogen,

C_1-C_{10}alkyl, arylC_0-C_{10}alkyl, or R_{22} and R_{23} are taken together with the nitrogen to which they are attached forming a cyclic system containing 3 to 8 carbon atoms with at least one substituent as defined above.

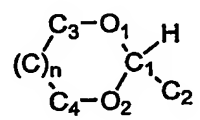
The definition of saturated heterocyclic includes but is not limited to pyrrolidinyl, pyrazolidinyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithienyl, thiomorpholinyl, piperazinyl, quinuclidinyl and the like.

The term "alpha-beta-unsaturated carbonyl" refers to a molecule that has a carbonyl group directly attached to a double or triple bonded carbon and which would be obvious to one of ordinary skill and knowledge in the art. The definition of alpha-beta-unsaturated carbonyl heterocyclic includes but is not limited to acrolein, methylvinyl ketone, and the like.

The term "acetal" refers to a molecule that contains a carbon atom C_1 that is directly attached to a hydrogen atom (H_1), a substituted carbon atom (C_2) and two oxygen atoms (O_1 and O_2). These oxygen atoms are in turn attached to other substituted carbon atoms (C_3 and C_4), which would be obvious to one of ordinary skill and knowledge in the art. The definition of acetal includes but is not limited to 1,1-dimethoxypropane, 1,1-bis-allyloxybutane and the like.

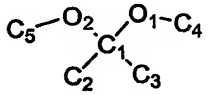


The term "cyclic acetal" refers to an acetal as defined above where C_3 and C_4, together with the oxygen atoms to which they are attached, combine thru an alkyl bridge to form a 5- to 10-membered ring, which would be obvious to one of ordinary skill and knowledge in the art. The definition of cyclic acetal includes but is not limited to 2-methyl-[1,3]dioxolane, 2-ethyl-[1,3]dioxane, 2-phenyl-[1,3]dioxane, 2 2-phenyl-hexahydro-pyrano[3,2-d][1,3]dioxine and the like.

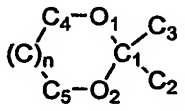


n = 1 to 5

The term "ketal" refers to a molecule that contains a carbon atom C_1 that is directly attached to two substituted carbon atom (C_2 and C_3) and two oxygen atoms (O_1 and O_2). These oxygen atoms are in turn attached to other substituted carbon atoms (C_4 and C_5), which would be obvious to one of ordinary skill and knowledge in the art. The definition of acetal includes but is not limited to 2,2-dimethoxy-butane, 3,3-diethoxy-pentane and the like.



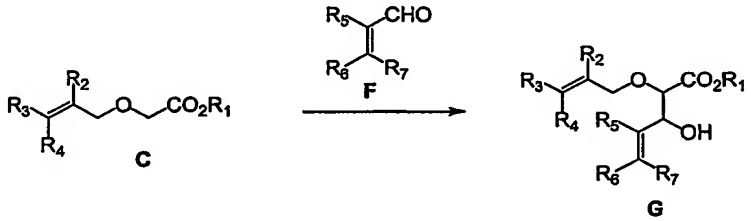
The term "cyclic ketal" refers to a ketal as defined above where C_4 and C_5, together with the oxygen atoms to which they are attached, combine thru an alkyl bridge to form a 5- to 10-membered ring, which would be obvious to one of ordinary skill and knowledge in the art. The definition of cyclic acetal includes but is not limited to 2,2,4,5-tetramethyl-[1,3]dioxolane, 2,2-diethyl-[1,3]dioxepane, 2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine and the like.



n = 1 to 5

Detailed Description

In one embodiment, the present invention provides a process for preparing a compound of formula **G**. Such a process can be performed, for example, by contacting a compound of formula **C** with a compound of formula **F** under conditions suitable to form compound of formula **G**, as set forth below:



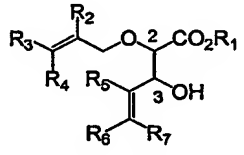
In the scheme shown above, R_1 is typically alkyl, substituted alkyl, or aryl; R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl and aryl; R_3, R_4, R_6 and R_7 are

either all hydrogen or, of R_3, R_4, R_6 and R_7, three are hydrogen and the fourth is alkyl, substituted alkyl, or aryl. In one embodiment, R_1 is ethyl and R_2, R_3, R_4, R_6, and R_7 are hydrogen. In another embodiment, R_1 is ethyl, R_5 is methyl, and R_2, R_3, R_4, R_6, and R_7 are hydrogen. In still another embodiment, R_1 is ethyl, R_5 is phenyl, and R_2, R_3, R_4, R_6, and R_7 are hydrogen.

Solvents contemplated for use in the practice of this particular invention process are typically ethereal solvents, such as for example, diethyl ether, dioxane, tetrahydrofuran, and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about –100°C up to about 30°C.

Compound **C** is typically contacted with compound **F** in the presence of an organometallic reagent. Organometallic reagents contemplated for use include, for example, lithium diisopropyl amide, tert-butyl lithium, lithium hexamethyldisilazide, sodium hexamethyldisilazide, potassium hexamethyldisilazide, lithium diisopropyl amide-spartein complex, triethyl amine-dicyclohexyl boron triflate complex, and the like.

In yet another embodiment of the invention, there are provided compounds having the structure **G**:



G

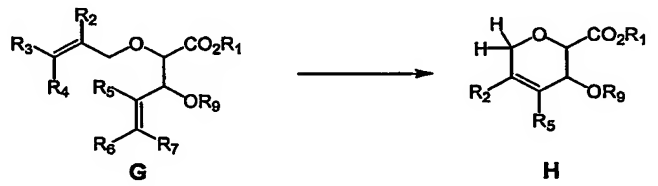
wherein:

R_1 is alkyl, substituted alkyl, or aryl, R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl and aryl; R_3, R_4, R_6 and R_7 are either all hydrogen or, of R_3, R_4, R_6 and R_7, three are hydrogen and the fourth is alkyl, substituted alkyl, or aryl. In one embodiment, R_1 is ethyl and R_2, R_3, R_4, R_5, R_6, and R_7 are hydrogen.

Invention compounds having structure **G** maybe optically pure and include (2R,3R)-2-allyloxy-3-hydroxy-pent-4-enoic acid ethyl ester; (2S,3S)-2-allyloxy-3-hydroxy-

pent-4-enoic acid ethyl ester; (2R,3S)-2-allyloxy-3-hydroxy-pent-4-enoic acid ethyl ester; and (2S,3R)-2-allyloxy-3-hydroxy-pent-4-enoic acid ethyl ester.

In one embodiment, the present invention provides a process for preparing a compound of formula **H**. Such a process can be performed, for example, by contacting a compound of formula **G** under conditions suitable to form compound of formula **H**, as set forth below:



G **H**

In the scheme shown above, R_1 is typically alkyl, substituted alkyl, or aryl; R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl and aryl; R_3, R_4, R_6 and R_7 are either all hydrogen or, of R_3, R_4, R_6 and R_7, three are hydrogen and the fourth is alkyl, substituted alkyl, or aryl; R_9 is hydrogen, alkyl, substituted alkyl, aryl or hydroxyl protecting group. In another embodiment, R_1 is ethyl, and R_2, R_3, R_4, R_5, R_6, R_7 and R_9 are hydrogen. In another embodiment, R_1 is ethyl, R_6 is methyl, and R_2, R_3, R_4, R_5, R_7 and R_9 are hydrogen. In still another embodiment, R_1 is ethyl, R_6 is phenyl, and R_2, R_3, R_4, R_5, R_7 and R_9 are hydrogen.

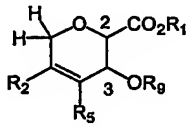
In one embodiment, the present invention provides a process for preparing compound of formula **H** as a mixture of stereoisomers, such as for example, cis or trans stereoisomers and the like. In another embodiment, the invention provides a process for separating such stereoisomers, such as for example, chromatography, crystallization, re-crystallization, distillation and the like. In still another embodiment, the invention provides a process for preparing compound **H** as an optically pure isomer.

Solvents contemplated for use in the practice of this particular invention process are typically water, halogenated solvents, such as for example, dichloromethane, dichloroethane and the like, ethereal solvents, such as for example, diethyl ether, dioxane, tetrahydrofuran and the like, polar non-protic solvents, such as for example, acetonitrile, dimethyl formamide, dimethyl acetamide, N-methylpyrrolidine, dimethyl

sulfoxide and the like, aromatic solvents, such as for example, benzene, toluene, dichlorobenzene, xylene and the like, alcoholic solvents, such as for example, methanol, ethanol, isopropanol and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about 0°C up to about 150°C.

Compound **G** is typically contacted with a ring-closing metathesis catalyst. Ring-closing metathesis catalysts contemplated for use include, for example, 2,6-diisopropylphenylimidoneophylidene molybdenum (IV) bis-(tert-butoxide), 2,6-diisopropylphenylimidoneophylidene molybdenum (IV) bis-(hexafluoro-tert-butoxide), 2,6-diisopropylphenylimidoneophylidene[racemic-BIPHEN] molybdenum (IV), 2,6-diisopropylphenylimidoneophylidene[(R)-(+)-BIPHEN] molybdenum (IV), 2,6-diisopropylphenylimidoneophylidene[(S)-(-)-BIPHEN] molybdenum (IV), bis-(tricyclohexylphosphine)benzylidine ruthenium (IV) dichloride, bis-(tricyclohexylphosphine)-3-methyl-2-butenylidene ruthenium (IV) dichloride, bis-(tricyclopentylphosphine)benzylidine ruthenium (IV) dichloride, bis-(tricyclopentylphosphine)-3-methyl-2-butenylidene ruthenium (IV) dichloride, tricyclohexylphosphine-(1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene)-benzylidine ruthenium (IV) dichloride, tricyclohexylphosphine-(1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene)-benzylidine ruthenium (IV) dichloride, (1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene)-2-isopropoxyphenylmethylene ruthenium (IV) dichloride, (tricyclopentylphosphine)-2-isopropoxyphenylmethylene ruthenium (IV) dichloride, (tricyclopentylphosphine)-2-methoxy-3-naphthylmethylene ruthenium (IV) dichloride and the like.

In yet another embodiment of the invention, there are provided compounds having the structure **H**:



H

wherein:

R_1 is alkyl, substituted alkyl, or aryl; R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl and aryl; R_9 is hydrogen, alkylcarbonyl, substituted alkylcarbonyl, arylcarbonyl or hydroxyl protecting group.

Invention compounds having structure **H** maybe optically pure and include 3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester, (2R,3R)-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester, (2S,3S)-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester, (2S,3R)-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester, (2R,3S)-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester, (2R,3R) 3-acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester, (2S,3S) 3-acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester, (2R,3S) 3-acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester, (2S,3R) 3-acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester

In one embodiment, the present invention provides a process for preparing a compound of formula **H**. Such a process can be performed, for example, by contacting a compound of formula **I** with a resolving enzyme and an acylating agent under conditions suitable to form compound of formula **H**, as set forth below:

In the scheme shown above, R_1 is typically alkyl, substituted alkyl, or aryl; R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl and aryl; R_9 is hydrogen, alkylcarbonyl, substituted alkylcarbonyl, or arylcarbonyl. In another embodiment, R_1 is ethyl, R_2 and R_5 are hydrogen, and R_9 is hydrogen or acetyl.

Solvents contemplated for use in the practice of this particular invention process are typically water, halogenated solvents, such as for example, dichloromethane, dichloroethane and the like, ethereal solvents, such as for example, diethyl ether, dioxane, tetrahydrofuran and the like, polar non-protic solvents, such as for example, acetonitrile, dimethyl formamide, dimethyl acetamide, N-methylpyrrolidine, dimethyl sulfoxide and the like, aromatic solvents, such as for example, benzene, toluene, dichlorobenzene, xylene and the like, alcoholic solvents, such as for example, methanol, ethanol, isopropanol and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about 0°C up to about 40°C.

Compound **I** is typically contacted with a resolving enzyme in the presence of an acylating agent. Resolving enzymes contemplated for use include lipase, esterase, peptidase, acylase or protease enzymes of mammalian, plant, fungal or bacterial origin, such as for example, Lipase Amano lipase PS-D (immobilized lipase from *Pseudomonas cepacia*), Amano Lipase PS-C (immobilized lipase from *Pseudomonas cepacia*), Roche Chirazyme L-3 (lipase, lyophilizate, from *Candida Rugosa)*, Roche Chirazyme L-3 (purified lipase, lyophilizate, from *Candida Rugosa*), Roche Chirazyme L-3 (purified lipase, carrier-fixed, carrier 2, lyophilizate, from *Candida rugosa*), Roche Chirazyme L-5 (lipase, solution, from *Candida antartica, type A)*, Roche Chirazyme L-5 (lipase, lyophilizate, from *Candida antartica, type A*), Roche Chirazyme L-5 (lipase, carrier-fixed, carrier 1, lyophilizate, from *Candida antartica, type A)*, Roche Chirazyme L-10 (lipase, lyophilizate, from *Alcaligenes sp.*), Altus Biologics 8 (lipase from *Mucor miehei*) and Altus Biologics 27 (lipase from *Alcaligenes sp.*) and the like. Acylating agents contemplated for use include, for example, ethyl acetate, vinyl acetate, vinyl propionate, vinyl butyrate, isopropenyl acetate, 1-ethoxyvinyl acetate, trichloroethyl butyrate, trifluoroethyl butyrate, trifluoroethyl laureate, S-ethyl thiooctanoate, biacetyl monooxime acetate, acetic anhydride, succinic anhydride, amino acid, diketene and the like.

In one embodiment, the present invention provides a process for preparing compound of formula **H** as a mixture of optically pure compounds, such as for example, a mixture of (2R,3R) 3-acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester and (2S,3S) 3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester, or a mixture of (2S,3R) 3-acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester and (2R,3S) 3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester. In another embodiment, the invention provides a process for separating such optically pure compounds, such as for example, chromatography, crystallization, re-crystallization, distillation and the like.

In one embodiment, the present invention provides a process for preparing a compound of formula **J**. Such a process can be performed, for example, by contacting a compound of formula **H** under conditions suitable to form compound of formula **J**, as set forth below:

H **J**

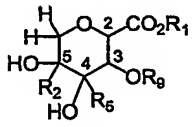
In the scheme shown above, R_1 is typically alkyl, substituted alkyl, or aryl; R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl and aryl; R_9 is hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl or hydroxyl protecting group. In another embodiment, R_1 is ethyl, R_2 and R_5 are hydrogen, and R_9 is hydrogen or acetyl.

Solvents contemplated for use in the practice of this particular invention process are typically water, halogenated solvents, such as dichloromethane and the like, alcoholic solvents, such as for example 2-methyl-2-propanol and the like, ethereal solvents, such as for example tetrahydrofuran and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about -78°C up to about 60°C.

Compound **H** is typically contacted with a suitable mixture of an oxidant, a co-oxidant and a ligand, or any suitable mixtures thereof. Oxidants contemplated for use include, for example, osmium tetroxide, potassium permanganate, thallium acetate, potassium periodate, silver acetate and the like, co-oxidants contemplated for use include, for example, N-methylmorpholine oxide, trimethylamine oxide, tert-butyl peroxide, iodine, potassium ferricyanide and the like, ligands contemplated for use include, for example, pyridine, quinuclidine, dihydroquinine acetate, dihydroquinidine acetate, dihydroquinine anthraquinone-1,4-diyl diether ($(DHQ)_2AQN$), dihydroquinine phthalazine-1,4-diyl diether ($(DHQ)_2PHAL$), dihydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether ($(DHQ)_2PYR$), dihydroquinidine anthraquinone-1,4-diyl diether ($(DHQD)_2AQN$), dihydroquinidine phthalazine-1,4-diyl diether ($(DHQD)_2PHAL$), dihydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether ($(DHQD)_2PYR$), tetraethyl

ammonium hydroxide, tetraethyl ammonium acetate, N,N,N'N'-tetramethylethylene diamine (TMEDA) and the like.

In yet another embodiment of the invention, there are provided compounds having the structure **J**:



J

wherein:

R_1 is hydrogen, alkyl, substituted alkyl, or aryl; R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9 is hydrogen, alkyl, substituted alkyl, substituted alkylcarbonyl, alkylcarbonyl, aryl, arylcarbonyl or hydroxyl protecting group.

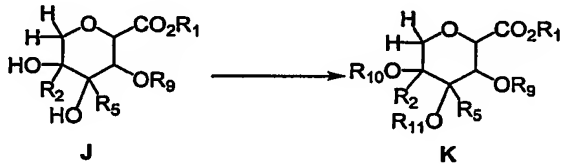
With the proviso that:

stereoisomers (2R,3R,4S,5S), (2R,3S,4S,5R), (2R,3R,4R,5R), (2R,3R,4S,5R), (2S,3R,4R,5R) cannot have R_1 = hydrogen or methyl and $R_2 = R_5 = R_9$ = hydrogen; and, stereoisomer (2S,3S,4R,5R) cannot have R_1 = hydrogen or methyl and $R_2 = R_5 = R_9$ = hydrogen;

Invention compounds having structure **J** maybe optically pure and include (1R,2R,3R,4R) 3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester; (1R,2R,3S,4S) 3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester; (1S,2S,3R,4R) 3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester; (1S,2S,3S,4S) 3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester; (1R,2S,3R,4R) 3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester; (1R,2S,3S,4S) 3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester; (1S,2R,3R,4R) 3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester; (1S,2R,3S,4S) 3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester; (1R,2R,3R,4R) 3-4,5-trihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester; (1R,2R,3S,4S) 3-4,5-trihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester; (1S,2S,3R,4R) 3-4,5-trihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester; (1S,2S,3S,4S) 3-4,5-trihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester; (1R,2S,3R,4R) 3-4,5-trihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester; (1R,2S,3S,4S) 3-4,5-trihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester;

(1S,2R,3R,4R) 3-4,5-trihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester; and
(1S,2R,3S,4S) 3-4,5-trihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester.

In one embodiment, the present invention provides a process for preparing a compound of formula **K**. Such a process can be performed, for example, by contacting a compound of formula **J** under conditions suitable to form a compound of formula **K**, as set forth below:



In the scheme shown above, R_1 is typically alkyl, substituted alkyl, or aryl; R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl and aryl; R_9, R_{10} and R_{11} are each independently hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl and hydroxyl protecting group.

Solvents contemplated for use in the practice of this particular invention process are typically water, halogenated solvents, such as for example, dichloromethane, dichloroethane and the like, ethereal solvents, such as for example, diethyl ether, dioxane, tetrahydrofuran and the like, polar non-protic solvents, such as for example, acetonitrile, dimethyl formamide, dimethyl acetamide, N-methylpyrrolidine, dimethyl sulfoxide and the like, aromatic solvents, such as for example, benzene, toluene, dichlorobenzene, xylene and the like, alcoholic solvents, such as for example, methanol, ethanol, isopropanol and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about 0°C up to about 40°C.

Compound **J** is typically contacted with a resolving enzyme in the presence of an acylating agent. Resolving enzymes contemplated for use include lipase, esterase, peptidase, acylase or protease enzymes of mammalian, plant, fungal or bacterial origin, such as for example, Lipase Amano lipase PS-D (immobilized lipase from *Pseudomonas cepacia*), Amano Lipase PS-C (immobilized lipase from *Pseudomonas cepacia*), Roche Chirazyme L-3 (lipase, lyophilizate, from *Candida Rugosa)*, Roche Chirazyme L-3 (purified lipase, lyophilizate, from *Candida Rugosa*), Roche Chirazyme L-3 (purified lipase, carrier-fixed, carrier 2, lyophilizate, from *Candida rugosa*), Roche Chirazyme L-5

(lipase, solution, from *Candida antartica, type A)*, Roche Chirazyme L-5 (lipase, lyophilizate, from *Candida antartica, type A*), Roche Chirazyme L-5 (lipase, carrier-fixed, carrier 1, lyophilizate, from *Candida antartica, type A)*, Roche Chirazyme L-10 (lipase, lyophilizate, from *Alcaligenes sp.*), Altus Biologics 8 (lipase from *Mucor miehei*) and Altus Biologics 27 (lipase from *Alcaligenes sp.*) and the like. Acylating agents contemplated for use include, for example, ethyl acetate, vinyl acetate, vinyl propionate, vinyl butyrate, isopropenyl acetate, 1-ethoxyvinyl acetate, trichloroethyl butyrate, trifluoroethyl butyrate, trifluoroethyl laureate, S-ethyl thiooctanoate, biacetyl monooxime acetate, acetic anhydride, succinic anhydride, amino acid, diketene and the like.

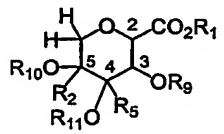
Compound **J** can also be contacted with an electrophilic reagent. Electrophilic reagents contemplated for use include, for example, diazomethane, trimethylsilyldiazomethane, alkyl halides, such as for example methyl iodide, benzyl bromide and the like, alkyl triflates, such as for example methyl triflate and the like, alkyl sulfonates, such as for example ethyl toluenesulfonate, butyl methanesulfonate and the like, acyl halides, such as for example acetyl chloride, benzoyl bromide and the like, acid anhydrides, such as for example acetic anhydride, succininc anhydride, maleic anhydride and the like, isocyanates, such as for example methyl isocyanate, phenylisocyanate and the like, chloroformates, such as for example methyl chloroformate, ethyl chloroformate, benzyl chloroformate and the like, sulfonyl halides, such as for example methanesulfonyl chloride, p-tolunesulfonyl chloride and the like, silyl halides, such as for example trimethylsilyl chloride, tertbutyldimethyl silyll chloride and the like, phosphoryl halide such as for example dimethyl chlorophosphate and the like, alpha-beta-unsaturated carbonyl such as for example acrolein, methyl vinyl ketone, cinnamaldehyde and the like.

Compound **J** can also be contacted with an alcohol in the presence of an azodicarboxylate and a phosphine base, or any suitable mixtures thereof. Azodicarboxylates contemplated for use include, for example, diethyl azodicarboxylate, dicyclohexyl azodicarboxylate, diisopropyl azodicarboxylate and the like. Phosphine bases contemplated for use include, for example, triethylphosphine, tricyclopentylphosphine, tricyclohexylphosphine, triphenylphosphine, tri-o-tolylphosphine, and the like.

Compound **J** can also be contacted with a carboxylic acid or an amino acid in the presence of a coupling agent and a base, or any suitable mixtures thereof. Coupling agents contemplated for use include, for example, dicyclohexylcarbodiimide (DCC), diisopropyl carbodiiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDCI), N-hydroxybenzotriazole (HOBT), N-hydroxysuccinimide (HOSu), 4-nitrophenol, pentafluorophenol, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), O-benzotriazole-N,N,N'N'-tetramethyluronium hexafluorophosphate (HBTU), benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP), benzotriazole-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate, bromo-trispyrrolidino- phosphonium hexafluorophosphate, 2-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU), O-(N-succinimidyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TSTU), tetramethylfluoroformamidinium hexafluorophosphate and the like. Bases contemplated for use include, for example, triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine, and the like.

In another embodiment, the present invention provides a process for preparing compound of formula **K** as a mixture of optically pure compounds, such as for example, (2R,3R,4R,5R)-3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester and (2R,3R,4S,5S)-3,5-diacetoxy-4-hydroxy-tetrahydropyran-2-carboxylic acid ethyl ester. In another embodiment, the invention provides a process for separating such optically pure compounds, such as for example, chromatography, crystallization, re-crystallization, distillation and the like.

In yet another embodiment of the invention, there are provided compounds having the structure **K**:



K

wherein:

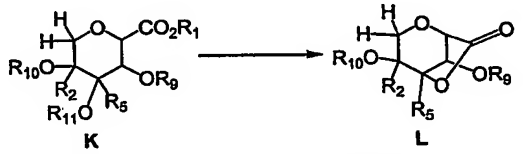
R_1 is alkyl, substituted alkyl, or aryl; R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl and aryl; R_9, R_{10} and R_{11} are

each independently hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl and hydroxyl protecting group.

With the proviso that

stereoisomers (2R, 3R, 4S, 5S), (2R, 3S, 4S, 5R), (2R, 3R, 4R, 5R), (2R, 3R, 4S, 5R), (2S, 3R, 4R, 5R), (2S, 3S, 4R, 5S), (2R, 3S, 4R, 5S) cannot have R_1 = methyl and R_2 = R_5 = hydrogen and R_9 = R_{10} = R_{11} = acetyl; stereoisomers (2R, 3R, 4S, 5S), (2R, 3S, 4S, 5R), (2R, 3R, 4R, 5R), (2R, 3R, 4S, 5R), (2S, 3R, 4R, 5R), (2S, 3S, 4R, 5R) cannot have R_1 = methyl and R_2 = R_5 = R_9 = R_{10} = R_{11} = hydrogen; stereoisomers (2R, 3R, 4S, 5S), (2R, 3S, 4S, 5R), (2R, 3R, 4R, 5R), (2R, 3R, 4S, 5R), (2S, 3R, 4R, 5R), (2S, 3S, 4R, 5R) cannot have R_1 = R_2 = R_5 = R_9 = R_{10} = R_{11} = hydrogen; stereoisomers (2S, 3S, 4R, 5R), (2R, 3S, 4R, 5R) cannot have R_1 = R_{10} = R_{11} = methyl and R_2 = R_5 = hydrogen and R_9 = acetyl; stereoisomers (2S, 3S, 4R, 5R), (2R, 3S, 4R, 5R) cannot have R_1 = R_{10} = R_{11} = methyl and R_2 = R_5 = hydrogen and R_9 = benzoyl; stereoisomer (2S, 3R, 4R, 5S) cannot have R_1 = R_2 = R_5 = hydrogen and R_9 = R_{10} = R_{11} = acetyl; and stereoisomer (1S, 4R, 5R, 8S) cannot have R_1 = methyl R_2 = R_5 = R_{11} = hydrogen and R_9 = R_{10} = benzyl.

In one embodiment, the present invention provides a process for preparing a compound of formula **L**. Such a process can be performed, for example, by contacting a compound of formula **K** under conditions suitable to form a compound of formula **L**, as set forth below:



In the scheme shown above, R_1 is typically alkyl, substituted alkyl, or aryl; R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl and aryl; R_9 and R_{10} are each independently hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl and hydroxyl protecting group; R_{11} is hydrogen.

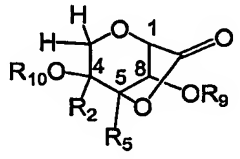
Solvents contemplated for use in the practice of this particular invention process are typically water, halogenated solvents, such as for example, dichloromethane, dichloroethane and the like, ethereal solvents, such as for example, diethyl ether, dioxane, tetrahydrofuran and the like, polar non-protic solvents, such as for example,

acetonitrile, dimethyl formamide, dimethyl acetamide, N-methylpyrrolidine, dimethyl sulfoxide and the like, aromatic solvents, such as for example, benzene, toluene, dichlorobenzene, xylene and the like, alcoholic solvents, such as for example, methanol, ethanol, isopropanol and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about 0°C up to about 200°C.

In one embodiment, compound **K** is contacted with focused microwave radiation. The process is typically carried out using a quartz reactor at a pressure in the range of about 1 atm to about 25 atm and a power setting in the range of about 1 W per liter of solvent to about 900 W per liter of solvent.

In another embodiment, compound **K** is contacted with a dehydrating reagent in the presence or absence of a base. Dehydrating reagents contemplated for use include, for example, acetic acid, hydrochloric acid, sulfuric acid, toluenesulfonic acid, acetyl chloride, benzoyl chloride, oxalyl chloride, acetic anhydride, methyl chloroformate, dicyclohexylcarbodiimide, diethyl azodicarboxylate, 2,4,6-trichloro-[1,3,5]triazine, dibutyltin oxide, dibutyltin chloride, zinc chloride, molecular sieves, silica gel, alumina, catechol borane, mercuric acetate, silver perchlorate and the like. Bases contemplated for use include, for example, pyridine, triethylamine, diisopropylethylamine, triphenylphosphine, imidazole, tert-butyl lithium, tert-butyl magnesium chloride, potassium hydride, sodium hydride, potassium tert-butoxide, sodium methoxide, potassium carbonate, potassium bicarbonate, sodium carbonate, cesium carbonate, potassium hydroxide, sodium hydroxide and the like.

In yet another embodiment of the Invention, there are provided compounds having the structure **L**:



L

wherein:

R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl and aryl; R_9 and R_{10} are each Independently hydrogen, alkyl, substituted

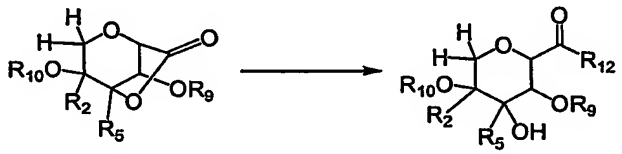
alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl and hydroxyl protecting group.

With the proviso that:

stereoisomer (1S, 4R, 5R, 8S) cannot have $R_2 = R_5 = R_9 = R_{10}$ = hydrogen; stereoisomer (1S, 4R, 5R, 8S) cannot have $R_2 = R_5 = R_{10}$ = hydrogen and R_9 = benzoyl; stereoisomer (1S, 4R, 5R, 8S) cannot have $R_2 = R_5$ = hydrogen and $R_9 = R_{10}$ = benzoyl; stereoisomer (1S, 4R, 5R, 8S) cannot have $R_2 = R_5$ = hydrogen and $R_9 = R_{10}$ = benzyl

Invention compounds having structure **L** maybe optically pure and include (1R,4S,5S,8R)-8-acetoxy-4-hydroxy-2,6-dioxa-bicyclo[3.2.1]octan-7-one and (1R,4S,5S,8R)-4,8-hydroxy-2,6-dioxa-bicyclo[3.2.1]octan-7-one.

In one embodiment, the present invention provides a process for preparing a compound of formula **M**. Such a process can be performed, for example, by contacting a compound of formula **L** with a nucleophile under conditions suitable to form a compound of formula **M**, as set forth below:



L **M**

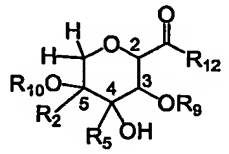
R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl and aryl; R_9 and R_{10} are each independently hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl and hydroxyl protecting group; R_{12} is typically alkyl, substituted alkyl, aryl, hydroxy, alkyloxy, substituted alkyloxy, aryloxy, amino, alkylamino, arylamino, hydrazine, alkylhydrazino, arylhydrazino, alkylcarbonylhydrazino, arylcarbonylhydrazino, nitrogen containing saturated heterocyclic compound, O-protected amino acid, or solid support; with the proviso that compound of formula **L** cannot be the stereoisomer (1S,4R,5R,8S) where $R_2 = R_5$ = hydrogen and $R_9 = R_{10}$ = benzyl and R_{12} = methoxy.

Solvents contemplated for use in the practice of this particular invention process are typically water, halogenated solvents, such as for example, dichloromethane, dichloroethane and the like, ethereal solvents, such as for example, diethyl ether, dioxane, tetrahydrofuran and the like, polar non-protic solvents, such as for example, acetonitrile, dimethyl formamide, dimethyl acetamide, N-methylpyrrolidine, dimethyl sulfoxide and the like, aromatic solvents, such as for example, benzene, toluene, dichlorobenzene, xylene and the like, alcoholic solvents, such as for example, methanol, ethanol, isopropanol and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about 0°C up to about 150°C.

Compound L is typically contacted with a nucleophile in the presence or absence of a Lewis acidic reagent. Nucleophiles contemplated for use include, for example, water, potassium hydroxide, methanol, sodium ethoxide, benzyl alcohol, 3,5-dimethylphenol, sodium phenoxide, ethyl thiol, potassium phenyl thiolate, ammonia, ammonium hydroxide, methylamine, benzylamine, dibutylamine, aniline, 3-methoxyaniline, diphenylamine, sodium amide, Lithium dimethylamide, potassium benzylmethylamide, lithium anilide, hydrazine, potassium hydrizide, methylhydrazine, phenylhydrazine, benzoylhydrazine, acetylhydrazine, piperidine, morpholine, piperazine, thiomorpholine, pyrrolidine, lithium piperidide, potassium morpholinide, glycine methyl ester, serine tert-butyl ester, valine ethyl ester lithium salt, methyl lithium, ethyl magnesium bromide, phenyl lithium, diethyl zinc, diethyl mercury, trimethyl aluminum, triethyl indium, trimethyl gallium, Merrifield resin, Wang resin, Rink resin, Wang resin lithium salt and the like. Lewis acidic reagents contemplated for use include, for example, boron trifluoride, boron trifluoride etherate, boron trifluoride tetrahydrofuran complex, boron trifluoride tert-butyl-methyl ether complex, boron trifluoride dibutyl ether complex, boron trifluoride dihydrate, boron trifluoride di-acetic acid complex, boron trifluoride dimethyl sulfide complex, boron trichloride, boron trichloride dimethyl sulfide complex, boron tribromide, boron tribromide dimethyl sulfide complex, boron triiodide, trimethoxyborane, triethoxyborane, trimethylaluminum, triethylaluminum, aluminum trichloride, aluminum trichloride tetrahydrofuran complex, aluminum tribromide, titanium tetrachloride, titanium tetrabromide, titanium iodide, titanium tetraethoxide, titanium tetraisopropoxide, scandium (III) trifluoromethanesulfonate, yttrium (III) trifluoromethanesulfonate, ytterbium (III) trifluoromethanesulfonate, lanthanum (III) trifluoromethanesulfonate, zinc (II) chloride, zinc (II) bromide, zinc (II) iodide, zinc (II)

trifluoromethanesulfonate, zinc (II) sulfate, magnesium sulfate, lithium perchlorate, copper (II) trifluoromethanesulfonate, copper (II) tetrafluoroborate and the like.

In yet another embodiment of the invention, there are provided compounds having the structure **M**:



M

wherein:

R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl and aryl; R_9 and R_{10} are each independently hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl and hydroxyl protecting group; R_{12} is alkyl, substituted alkyl, aryl, hydroxy, alkyloxy, substituted alkyloxy, aryloxy, amino, alkylamino, arylamino, nitrogen containing saturated heterocyclic compound, O-protected amino acid, or solid support.

With the proviso that:

stereoisomers (2R, 3R, 4S, 5S), (2R, 3S, 4S, 5R), (2R, 3R, 4R, 5R), (2R, 3R, 4S, 5R), (2S, 3R, 4R, 5R), (2S, 3S, 4R, 5R) cannot have R_{12} = hydroxy and $R_2 = R_5 = R_9 = R_{10}$ = hydrogen; stereoisomers (2R, 3R, 4S, 5S), (2R, 3S, 4S, 5R), (2R, 3R, 4R, 5R), (2R, 3R, 4S, 5R), (2S, 3R, 4R, 5R), (2S, 3S, 4R, 5R) cannot have R_{12} = methoxy and $R_2 = R_5 = R_9 = R_{10}$ = hydrogen; stereoisomers (2R, 3R, 4S, 5S), (2R, 3S, 4S, 5R), (2R, 3R, 4R, 5R), (2R, 3R, 4S, 5R), (2S, 3R, 4R, 5R), (2S, 3S, 4R, 5S) cannot have R_{12} = amino and $R_2 = R_5 = R_9 = R_{10}$ = hydrogen; and, stereoisomer (1S, 4R, 5R, 8S) cannot have $R_2 = R_5$ = hydrogen and $R_9 = R_{10}$ = benzyl and R_{12} = methoxy.

In one embodiment, the present invention provides a process for preparing a compound of formula **N**. Such a process can be performed, for example, by contacting a

compound of formula **H** under conditions suitable to form a compound of formula **N**, as set forth below:

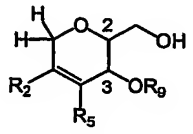
H **N**

R_1 is typically alkyl, substituted alkyl, or aryl; R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl and aryl; R_9 is hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, or hydroxyl protecting group. In another embodiment, R_1 is ethyl, R_2, R_5 and R_9 are hydrogen. In still another embodiment, R_1 is ethyl, R_2 and R_5 are hydrogen, and R_9 is acetyl.

Solvents contemplated for use in the practice of this particular invention process are typically water, ammonia, ethereal solvents, such as for example, diethyl ether, dioxane, tetrahydrofuran and the like, alcoholic solvents, such as for example, methanol, ethanol, isopropanol, 1,2-ethanediol, polyethylene glycol and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about -100°C up to about 100°C.

Compound **H** is typically contacted with a reducing reagent in the presence or absence of an acidic reagent or a Lewis acidic reagent. Reducing reagents contemplated for use include, for example, borane-dimethyl sulfide complex, 9-borabicyclo[3.3.1.]nonane (9-BBN), catechol borane, lithium borohydride, sodium borohydride, sodium borohydride-methanol complex, potassium borohydride, sodium hydroxyborohydride, lithium triethylborohydride, lithium n-butylborohydride, sodium cyanoborohydride, calcium (II) borohydride, lithium aluminum hydride, diisobutylaluminum hydride, n-butyl-diisobutylaluminum hydride, sodium bis-methoxyethoxyaluminum hydride, triethoxysilane, diethoxymethylsilane, lithium hydride, lithium, sodium, hydrogen Ni/B, and the like. Acidic reagents contemplated for use include, for example, acetic acid, methanesulfonic acid, hydrochloric acid, and the like. Lewis acidic reagents contemplated for use include, for example, trimethoxyborane, triethoxyborane, aluminum trichloride, lithium chloride, vanadium trichloride, dicyclopentadienyl titanium dichloride, cesium fluoride, potassium fluoride, zinc (II) chloride, zinc (II) bromide, zinc (II) iodide, and the like.

In yet another embodiment of the invention, there are provided compounds having the structure **N**:



N

wherein:

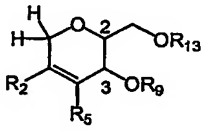
R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9 is hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, or hydroxyl protecting group

With the proviso that:

stereoisomers (2R,3S), (2S,3R) and (2R,3R) cannot have $R_2 = R_5 = R_9$ = hydrogen.

Invention compounds having structure **N** maybe optically pure and include (2S,3S)-2-hydroxymethyl-3,6-dihydro-2H-pyran-3-ol).

In yet another embodiment of the invention, there are provided compounds having the structure **O**:



O

wherein:

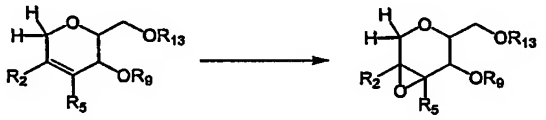
R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9 is alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, or hydroxyl protecting group; R_{13} is hydrogen, alkyl, substituted alkyl, aryl, alkylcarbonyl, arylcarbonyl, or hydroxyl protecting group.

With the proviso that:

stereoisomers (2R,3S), (2S,3R) and (2R,3R) cannot have $R_9 = R_{13}$ = acetyl; stereoisomer (2R,3S) cannot have R_9 = 2-bromoallyl and R_{13} = tert-butyldimethylsilyl; stereoisomer (2R,3S) cannot have R_9 = 2-bromobenzyl and R_{13} = tert-butyldimethylsilyl; stereoisomer (2R,3S) cannot have R_9 = 2-bromocyclopent-1-ene

and R_{13} = tert-butyldimethylsilyl; stereoisomer (2R,3S) cannot have R_9 = 2-bromocyclohex-1-ene and R_{13} = tert-butyldimethylsilyl; stereoisomer (2R,3S) cannot have R_9 = trichloromethylimidate [C(=NH)CCl_3] and R_{13} = acetyl; stereoisomer (2R,3S) cannot have R_9 = trichloromethylimidate [C(=NH)CCl_3] and R_{13} = tert-butyldimethylsilyl; stereoisomer (2R,3S) cannot have R_9 = 4-methoxyphenylaminocarboxy [4-$CH_3OC_6H_4NHC(=O)$] and R_{13} = benzoyl; stereoisomer (2R,3S) cannot have R_9 = 4-methoxyphenylaminocarboxy [4-$CH_3OC_6H_4NHC(=O)$] and R_{13} = tert-butyldimethylsilyl; stereoisomer (2S,3R) cannot have R_9 = allyl and R_{13} = tosyl; stereoisomer (2R,3R) cannot have R_9 = R_{13} = benzoyl; and, stereoisomer (2R,3R) cannot have R_9 = 2-bromoallyl and R_{13} = tert-butyldimethylsilyl

In one embodiment, the present invention provides a process for preparing a compound of formula **P**. Such a process can be performed, for example, by contacting a compound of formula **O** under conditions suitable to form a compound of formula **P**, as set forth below:



O **P**

In the scheme shown above, R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9 and R_{13} are each independently hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, and hydroxyl protecting group, with the proviso that stereoisomer (1S,4R,5R,6R) cannot have R_9 = hydrogen and R_{13} = tert-butyldimethylsilyl; and, stereoisomer (1S,4R,5R,6R) cannot have R_9 = hydrogen and R_{13} = tert-butyldiphenylsilyl.

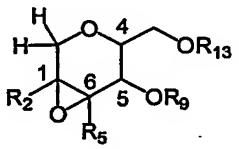
In another embodiment, compound of formula **O** is the (2R,3R) stereoisomer; R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9 and R_{13} are each independently hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, and hydroxyl protecting group.

In still another embodiment, compound of formula **O** is the (2S,3S) stereoisomer; R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9 and R_{13} are each independently hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, and hydroxyl protecting group.

Solvents contemplated for use in the practice of this particular invention process are typically water, halogenated solvents, such as for example, dichloromethane, dichloroethane and the like, ethereal solvents, such as for example, diethyl ether, dioxane, tetrahydrofuran and the like, polar non-protic solvents, such as for example, acetonitrile, dimethyl formamide, dimethyl acetamide, N-methylpyrrolidine, dimethyl sulfoxide and the like, aromatic solvents, such as for example, benzene, toluene, dichlorobenzene, xylene and the like, alcoholic solvents, such as for example, methanol, ethanol, isopropanol and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about -100°C up to about 100°C.

Compound **O** is typically contacted with an epoxidation reagent in the presence or absence of a transition metal reagent and in the presence or absence of a ligand. Epoxidation reagents contemplated for use include, for example, oxygen, tert-butyl hydroperoxide, meta-chloroperbenzoic acid, dimethyl dioxirane, oxone, sodium hypochlorite, sodium periodate, iodosylbenzene and the like. Transition metal reagents contemplated for use include, for example, titanium tetraisopropoxide, polymer supported cyclopentadienyl titanium trichloride, zirconium tetraethoxide, hafnium tetraisopropoxide, vanadium pentoxide, niobium pentaethoxide, tantalum pentaisopropoxide, manganese (II) trifluoromethanesulfonate, iron (III) acetylacetonate, molybdenum hexacarbonyl, ruthenium dichloride tris(triphenylphosphine), cobalt (II) trifluoromethanesulfonate, and the like. Ligands contemplated for use include, for example, (R,R) diethyl tartarate, (S,S) diethyl tartarate, N-ethyl ephedrine, N-methylprolinol, porphyrin, 2,2'-[[(1S,2S)-1,2-diphenyl-1,2-ethanediyl]-bis(nitrilomethylidyne)]bis[6-(1,1-dimethylethyl)-4-methyl-phenol, 2,2'-[[(1R,2R)-1,2-diphenyl-1,2-ethanediyl]-bis(nitrilomethylidyne)]bis[6-(1,1-dimethylethyl)-4-methyl-phenol, 2,2'-[(1R,2R)-1,2-cyclohexanediylbis[(E)-nitrilomethylidyne]]bis[6-(1,1-dimethylethyl)-4-methyl-phenol and the like.

In yet another embodiment of the invention, there are provided compounds having the structure **P**:



P

wherein:

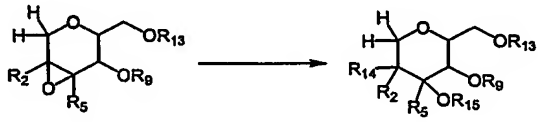
R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, or aryl; R_9 and R_{13} are each independently hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, or hydroxyl protecting group;

With the proviso that:

stereoisomer (1S,4R,5R,6R) cannot have R_9 = hydrogen and R_{13} = tert-butyldimethylsilyl; and, stereoisomer (1S,4R,5R,6R) cannot have R_9 = hydrogen and R_{13} = tert-butyldiphenylsilyl;

Invention compounds having structure **P** maybe optically pure and include stereoisomer (1R,4S,5S,6S) where R_2 = R_5 = R_9 = hydrogen and R_{13} = tert-butyldimethylsilyl; stereoisomer (1S,4S,5S,6R) where R_2 = R_5 = R_9 = hydrogen and R_{13} = tert-butyldimethylsilyl; stereoisomer (1R,4R,5R,6S) where R_2 = R_5 = R_9 = hydrogen and R_{13} = tert-butyldimethylsilyl; stereoisomer (1R,4S,5R,6S) where R_2 = R_5 = R_9 = hydrogen and R_{13} = tert-butyldimethylsilyl; stereoisomer (1S,4R,5S,6R) where R_2 = R_5 = R_9 = hydrogen and R_{13} = tert-butyldimethylsilyl; stereoisomer (1S,4S,5R,6R) where R_2 = R_5 = R_9 = hydrogen and R_{13} = tert-butyldimethylsilyl; stereoisomer (1R,4R,5S,6S) where R_2 = R_5 = R_9 = hydrogen and R_{13} = tert-butyldimethylsilyl.

In one embodiment, the present invention provides a process for preparing a compound of formula **Q**. Such a process can be performed, for example, by contacting a compound of formula **P** with a nucleophile under conditions suitable to form a compound of formula **Q**, as set forth below:



P **Q**

In the scheme shown above, R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9 is hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, or hydroxyl protecting group. R_{13} is alkyl, substituted alkyl and aryl, alkylcarbonyl, substituted alkylcarbonyl, arylcarbonyl, or hydroxyl protecting group. R_{14} is hydrogen, halogen, alkyl, substituted alkyl, aryl, heteroaryl, saturated heteroaryl, cyano, azido, amino, alkylamino, arylamino, hydrazine, alkylhydrazino, arylhydrazino, alkylcarbonylhydrazino, arylcarbonylhydrazino, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, alkylcarboxy, arylcarboxy, N-protected amino acid, O-

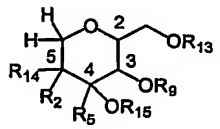
protected amino acid, or a solid support; and R_{15} is hydrogen. In another embodiment, R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9 is hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, or hydroxyl protecting group. R_{13} is alkyl, substituted alkyl and aryl, alkylcarbonyl, substituted alkylcarbonyl, arylcarbonyl, or hydroxyl protecting group, R_{14} is hydrogen; and R_{15} is hydrogen. In still another embodiment, R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9 is hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, or hydroxyl protecting group. R_{13} is alkyl, substituted alkyl and aryl, alkylcarbonyl, substituted alkylcarbonyl, arylcarbonyl, or hydroxyl protecting group, R_{14} is fluorine, chlorine, bromine or iodine, and R_{15} is hydrogen. In yet another embodiment, R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9 is hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, or hydroxyl protecting group. R_{13} is alkyl, substituted alkyl and aryl, alkylcarbonyl, substituted alkylcarbonyl, arylcarbonyl, or hydroxyl protecting group, R_{14} is cyano; and R_{15} is hydrogen, trimethylsilyl, or tert-butyldimethylsilyl.

Solvents contemplated for use in the practice of this particular invention process are typically water, halogenated solvents, such as for example, dichloromethane, dichloroethane and the like, ethereal solvents, such as for example, diethyl ether, dioxane, tetrahydrofuran and the like, polar non-protic solvents, such as for example, acetonitrile, dimethyl formamide, dimethyl acetamide, N-methylpyrrolidine, dimethyl sulfoxide and the like, aromatic solvents, such as for example, benzene, toluene, dichlorobenzene, xylene and the like, alcoholic solvents, such as for example, methanol, ethanol, isopropanol and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about -100°C up to about 150°C.

Compound **P** is typically contacted with a nucleophile in the presence or absence of a Lewis acidic reagent. Nucleophiles contemplated for use include, for example, water, potassium cyanide, trimethylsilyl cyanide, sodium azide, potassium iodide, sodium fluoride, potassium hydroxide, methanol, sodium ethoxide, benzyl alcohol, 3,5-dimethylphenol, sodium phenoxide, ethyl thiol, potassium phenyl thiolate, ammonia, ammonium hydroxide, hydrazine, ethyl hydrazine, phenyl hydrazine, benzoylhydrazine, methylamine, benzylamine, dibutylamine, aniline, 3-methoxyaniline, diphenylamine, sodium amide, Lithium dimethylamide, potassium benzylmethylamide, lithium anilide,

hydrazine, potassium hydrizide, methylhydrazine, phenylhydrazine, benzoylhydrazine, acetylhydrazine, piperidine, morpholine, piperazine, thiomorpholine, pyrrolidine, lithium piperidide, potassium morpholinide, phthalimide, maleimide, adenine, guanine, uracil, thymine, cytosine, imidazole, pyrrole, indole, tetrazole, glycine methyl ester, serine tert-butyl ester, valine ethyl ester lithium salt, N-benzylleucine, methyl lithium, ethyl magnesium bromide, phenyl lithium, diethyl zinc, diethyl mercury, trimethyl aluminum, triethyl indium, trimethyl gallium, Merrifield resin, Wang resin, Rink resin, Wang resin lithium salt, compound of formula **N** and the like. Lewis acidic reagents contemplated for use include, for example, boron trifluoride, boron trifluoride etherate, boron trifluoride tetrahydrofuran complex, boron trifluoride tert-butyl-methyl ether complex, boron trifluoride dibutyl ether complex, boron trifluoride dihydrate, boron trifluoride di-acetic acid complex, boron trifluoride dimethyl sulfide complex, boron trichloride, boron trichloride dimethyl sulfide complex, boron tribromide, boron tribromide dimethyl sulfide complex, boron triiodide, trimethoxyborane, triethoxyborane, trimethylaluminum, triethylaluminum, aluminum trichloride, aluminum trichloride tetrahydrofuran complex, aluminum tribromide, titanium tetrachloride, titanium tetrabromide, titanium iodide, titanium tetraethoxide, titanium tetraisopropoxide, scandium (III) trifluoromethanesulfonate, yttrium (III) trifluoromethanesulfonate, ytterbium (III) trifluoromethanesulfonate, lanthanum (III) trifluoromethanesulfonate, zinc (II) chloride, zinc (II) bromide, zinc (II) iodide, zinc (II) trifluoromethanesulfonate, zinc (II) sulfate, magnesium sulfate, lithium perchlorate, copper (II) trifluoromethanesulfonate, copper (II) tetrafluoroborate and the like.

In yet another embodiment of the invention, there are provided compounds having the structure **Q**:



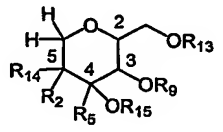
Q

wherein:

R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9 is hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, or hydroxyl protecting group; R_{13} is $-C(O)OR^8$, where R^8 is selected from the group consisting of alkyl, substituted alkyl and aryl and more

specifically R_8 is methyl, methoxymethyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloromethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 2-(trimethylsilyl)ethyl, 2-(phenylsulfonyl)ethyl, isobutyl, tert-Butyl, vinyl, allyl, 4-nitrophenyl, benzyl, 2-nitrobenzyl, 4-nitrobenzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 2-(methylthiomethoxy)ethyl, 2-dansenylethyl, 2-(4-nitrophenyl)ethyl, 2-(2,4-dinitrophenyl)ethyl, 2-cyano-1-phenylethyl, thiobenzyl, or 4-ethoxy-1-naphthyl; R_{14} is hydrogen, halogen, alkyl, substituted alkyl, aryl, heteroaryl, saturated heteroaryl, cyano, azido, amino, alkylamino, arylamino, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, alkylcarboxy, arylcarboxy, N-protected amino acid, O-protected amino acid, or a solid support; and R_{15} is hydrogen.

In yet another embodiment of the invention, there are provided compounds having the structure **Q**:



Q

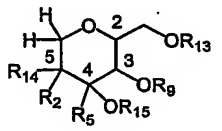
wherein:

R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9 is hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, or hydroxyl protecting group; R_{13} = -Si(R^8)$_3$, where R^8 is alkyl, substituted alkyl and aryl and more specifically R_{13} is trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, tribenzylsilyl, tri-p-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, di-tert-butylmethylsilyl, tris(trimethylsilyl)silyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, tert-butylmethoxyphenylsilyl, or tert-butoxydiphenylsilyl; R_{14} is hydrogen, halogen, alkyl, substituted alkyl, aryl, heteroaryl, saturated heteroaryl, cyano, azido, amino, alkylamino, arylamino, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, alkylcarboxy, arylcarboxy, N-protected amino acid, O-protected amino acid, or a solid support; and R_{15} is hydrogen.

With the proviso that:

stereoisomer (2R,3S,4R) cannot have R_9 = benzyl and $R_2 = R_5 = R_{14}$ = hydrogen and R_{13} = tert-butyldimethylsilyl; stereoisomer (2R,3S,4R) cannot have $R_9 = R_2 = R_5 = R_{14}$ = hydrogen and R_{13} = tert-butyldimethylsilyl; stereoisomer (2R,3S,4R) cannot have $R_9 = R_2 = R_5 = R_{14}$ = hydrogen and R_{13} = tert-butyldiphenylsilyl; stereoisomer (2R,3S,4S,5S) cannot have $R_2 = R_5 = R_9$ = hydrogen and R_{13} = tert-butyldiphenylsilyl and R_{14} = p-toluenecarboxy; stereoisomer (2R,3S,4S,5S) cannot have $R_2 = R_5 = R_9$ = hydrogen and R_{13} = tert-butyldimethylsilyl and R_{14} = tricholoroacetamide; and, stereoisomers (2R,3S,4S,5R) and (2S,3R,4R,5S) cannot have $R_2 = R_5 = R_9$ = hydrogen and R_{13} = tert-butyldimethylsilyl and R_{14} = 5,6-dichlorobenzimidazole.

In yet another embodiment of the invention, there are provided compounds having the structure **Q**:



Q

wherein:

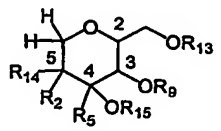
R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9 is hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, or hydroxyl protecting group; R_{13} is benzyl, 2-nitrobenzyl, 2-trifluoromethylbenzyl, 4-methoxybenzyl, 4-nitrobenzyl, 4-chlorobenzyl, 4-bromobenzyl, 4-cyanobenzyl, 4-phenylbenzyl, 4-acylaminobenzyl, 4-azidobenzyl, 4-(methylsulfinyl)benzyl, 2,4-dimethoxybenzyl, 4-azido-3-chlorobenzyl, 3,4-dimethoxybenzyl, 2,6-dichlorobenzyl, 2,6-difluorobenzyl, 1-pyrenylmethyl, diphenylmethyl, 4,4'-dinitrobenzhydryl, 5-benzosuberyl, triphenylmethyl (trityl), α-naphthyldiphenylmethyl, (4-methoxyphenyl)-diphenyl-methyl (MMT), di-(p-methoxyphenyl)-phenylmethyl, tri-(p-methoxyphenyl)methyl, 4-(4'-bromophenacyloxy)-phenyldiphenylmethyl, 4,4',4"-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4"-tris(levulinoyloxyphenyl)methyl, 4,4'-dimethoxy-3"-[N-(imidazolylmethyl)]trityl, 4,4'-

dimethoxy-3"-[N-(imidazolylethyl)carbamoyl]trityl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 4-(17-tetrabenzo[a,c,g,i]fluorenylmethyl)-4,4'-dimethoxytrityl, 9-anthryl, 9-(9-phenyl)xanthenyl, or 9-(9-phenyl-10-oxo)anthryl; R_{14} is hydrogen, halogen, alkyl, substituted alkyl, aryl, heteroaryl, saturated heteroaryl, cyano, azido, amino, alkylamino, arylamino, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, alkylcarboxy, arylcarboxy, N-protected amino acid, O-protected amino acid, or a solid support; and R_{15} is hydrogen.

With the proviso that:

stereoisomer (2R, 3S, 4S, 5R) cannot have $R_2 = R_5$ = hydrogen and R_9 = benzoyl and R_{13} = (4-methoxyphenyl)-diphenyl-methyl and R_{14} = N-(9H-purin-6-yl)-benzamide; stereoisomer (2R, 3S, 4S, 5R) cannot have $R_2 = R_5$ = hydrogen and R_9 = benzoyl and R_{13} = (4-methoxyphenyl)-diphenyl-methyl and R_{14} = 1H-pyrimidine-2,4-dione; stereoisomer (2R, 3S, 4S, 5R) cannot have $R_2 = R_5$ = hydrogen and R_9 = benzoyl and R_{13} = (4-methoxyphenyl)-diphenyl-methyl and R_{14} = N-(2-oxo-1,2-dihydro-pyrimidin-4-yl)-benzamide; stereoisomer (2R, 3S, 4S, 5R) cannot have $R_2 = R_5$ = hydrogen and R_9 = benzoyl and R_{13} = (4-methoxyphenyl)-diphenyl-methyl and R_{14} = N,N-dimethyl-N'-(6-oxo-6,9-dihydro-1H-purin-2-yl)-formamidine; stereoisomer (2R, 3S, 4R) cannot have $R_2 = R_5 = R_9 = R_{14}$ = hydrogen and R_{13} = triphenylmethyl; stereoisomer (2R, 3S, 4S) cannot have $R_2 = R_5 = R_9 = R_{14}$ = hydrogen and R_{13} = benzyl; stereoisomers (2R, 3S, 4R, 5R) and (2R, 3S, 4R, 5S) cannot have $R_2 = R_5 = R_9$ = hydrogen and R_{13} = triphenylmethyl and R_{14} = hydroxy; and, stereoisomer (2R, 3R, 4R) and (2S, 3S, 4S) cannot have $R_2 = R_9 = R_{14}$ = hydrogen and R_5 = methyl and R_{13} = triphenylmethyl.

In yet another embodiment of the invention, there are provided compounds having the structure **Q**:



Q

wherein:

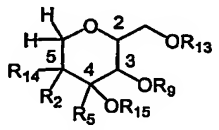
R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9 is hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, or hydroxyl protecting group; R_{13} is alkyl, substituted alkyl and aryl and more specifically R_{13} is methyl, tert-butyl, allyl, propargyl, p-chlorophenyl, p-methoxyphenyl, p-nitrophenyl, 2,4-dinitrophenyl, 2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl, methoxymethyl, methylthiomethyl, (phenyldimethylsilyl)methoxymethyl, benzyloxymethyl, p-methoxy-benzyloxymethyl, p-nitrobenzyloxymethyl, o-nitrobenzyloxymethyl, (4-methoxyphenoxy)methyl, guaiacolmethyl, tert-butoxymethyl, 4-pentenyloxymethyl, tert-butyldimethylsiloxymethyl, thexyldimethylsiloxymethyl, tert-butyldiphenylsiloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl, menthoxymethyl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-[2-(trimethylsilyl)ethoxy]ethyl, 1-methyl-1-ethoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 1-methyl-1-phenoxyethyl, 2,2,2-trichloroethyl, 1-dianisyl-2,2,2-trichloroethyl, 1,1,1,3,3,3-hexafluoro-2-phenylisopropyl, 2-trimethylsilylethyl, 2-(benzylthio)ethyl, 2-(phenylselenyl)ethyl, tetrahydropyranyl, 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydropyranyl S,S-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1-(2-fluorophenyl)-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, R_{14} is hydrogen, halogen, alkyl, substituted alkyl, aryl, heteroaryl, saturated heteroaryl, cyano, azido, amino, alkylamino, arylamino, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, alkylcarboxy, arylcarboxy, N-protected amino acid, O-protected amino acid, or a solid support; and R_{15} is hydrogen.

With the proviso that:

Compounds of formula **Q** cannot have $R_2 = R_5 = R_9$ = hydrogen and R_{13} = allyl and R_{14} = hydroxy; Compounds of formula **Q** cannot have $R_2 = R_5$ = hydrogen and $R_9 = R_{13}$ = methyl and R_{14} = methoxy; stereoisomer (2R,3S,4R,5S) cannot have $R_2 = R_5$ = hydrogen and $R_9 = R_{13}$ = methyl and R_{14} = methoxy; stereoisomer (2R,3S,4R,5S) cannot have $R_2 = R_5$ = hydrogen and R_9 = benzyl and R_{13} = methyl and R_{14} = hydroxy; stereoisomer (2R,3S,4R,5S) cannot have $R_2 = R_5$ = hydrogen and R_9 = benzyl and R_{13} = methyl and R_{14} = methoxy;

stereoisomer (2R,3S,4S,5S) cannot have $R_2 = R_5 = R_9$ = hydrogen and R_{13} = methyl and R_{14} = methoxy; stereoisomer (2R, 3S, 4R) cannot have $R_2 = R_5 = R_{14}$ = hydrogen and $R_9 = R_{13}$ = methyl.

In yet another embodiment of the invention, there are provided compounds having the structure **Q**:



Q

wherein:

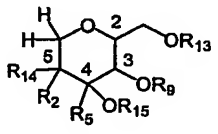
R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9 is hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, or hydroxyl protecting group; R_{13} is $-C(O)R^8$, where R^8 is alkyl, substituted alkyl, or aryl and more specifically R_8 is hydrogen, methyl, ethyl, tert-butyl, adamantyl, crotyl, chloromethyl, dichloromethyl, trichloromethyl, trifluoromethyl, methoxymethyl, triphenylmethoxymethyl, phenoxymethyl, 4-chlorophenoxymethyl, phenylmethyl, diphenylmethyl, 4-methoxycrotyl, 3-phenylpropyl, 4-pentenyl, 4-oxopentyl, 4,4-(ethylenedithio)pentyl, 5-[3-bis(4-methoxyphenyl)hydroxymethylphenoxy]- 4-oxopentyl, phenyl, 4-methylphenyl, 4-nitrophenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 4-phenylphenyl, 2,4,6-trimethylphenyl, α-naphthyl, benzoyl; R_{14} is hydrogen, halogen, alkyl, substituted alkyl, aryl, heteroaryl, saturated heteroaryl, cyano, azido, amino, alkylamino, arylamino, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, alkylcarboxy, arylcarboxy, N-protected amino acid, O-protected amino acid, or a solid support; and R_{15} is hydrogen.

With the proviso that:

stereoisomer (2R,3S,4R,5R) cannot have $R_2 = R_5 = R_9$ = hydrogen and R_{13} = acetyl and R_{14} = N-acetamido; stereoisomer (2R,3R,4S,5S) cannot have $R_2 = R_5 = R_9$ = hydrogen and R_{13} = acetyl and R_{14} = acetoxy; stereoisomer (2R,3S,4R) cannot have $R_2 = R_5 = R_{14}$ = hydrogen and $R_9 = R_{13}$ = tert-butylcarbonyl; stereoisomer (2R,3S,4R) cannot have $R_2 = R_5 = R_9$ =

R_{14} = hydrogen and R_{13} = 1-naphthoyl; stereoisomer (2R,3S,4R) cannot have R_2 = R_5 = R_9 = R_{14} = hydrogen and R_{13} = 2-naphthoyl; stereoisomer (2R,3S,4R) cannot have R_2 = R_5 = R_9 = R_{14} = hydrogen and R_{13} = benzoyl; stereoisomer (2R,3S,4R) cannot have R_2 = R_5 = R_9 = R_{14} = hydrogen and R_{13} = 4-methoxybenzoyl; stereoisomer (2R, 3S, 4S, 5R) cannot have R_2 = R_5 = R_9 = hydrogen and R_{13} = 3,4,5-trihydroxybenzoyl and R_{14} = (3,4,5-trihydroxyphenyl)carboxy; stereoisomer (2R, 3S, 4R, 5R) cannot have R_2 = R_5 = R_9 = hydrogen and R_{13} = benzoyl and R_{14} = phenylcarboxy; stereoisomer (2R, 3R, 4R, 5R) cannot have R_2 = R_5 = R_9 = hydrogen and R_{13} = benzoyl and R_{14} = phenylcarboxy; stereoisomer (2R, 3S, 4R, 5R) cannot have R_2 = R_5 = hydrogen and R_9 = R_{13} = benzoyl and R_{14} = phenylcarboxy; stereoisomer (2R, 3S, 4R, 5R) cannot have R_2 = R_5 = hydrogen and R_9 = R_{13} = benzoyl and R_{14} = hydroxy; compounds of formula **Q** cannot have R_2 = R_5 = R_9 = hydrogen and R_{13} = 3-(3,4,5-trimethoxyphenyl)acryloyl and R_{14} = hydroxy; compounds of formula **Q** cannot have R_2 = R_5 = R_9 = hydrogen and R_{13} = formyl and R_{14} = hydroxy; compounds of formula **Q** cannot have R_2 = R_5 = R_9 = hydrogen and R_{13} = ethylcarbonyl and R_{14} = hydroxy; compounds of formula **Q** cannot have R_2 = R_5 = R_9 = hydrogen and R_{14} = hydroxy and R_{13} = aminomethylcarbonyl; compounds of formula **Q** cannot have R_2 = R_5 = R_9 = hydrogen and R_{14} = hydroxy and R_{13} = 10-aminodecylcarbonyl; compounds of formula **Q** cannot have R_2 = R_5 = R_9 = hydrogen and R_{14} = hydroxy and R_{13} = 5-aminopentylcarbonyl; compounds of formula **Q** cannot have R_2 = R_5 = R_9 = hydrogen and R_{14} = hydroxy and R_{13} = succinoyl; and, compounds of formula **Q** cannot have R_2 = R_5 = R_9 = hydrogen and R_{13} = 3,4,5-trihydroxybenzoyl and R_{14} = hydroxy.

In yet another embodiment of the invention, there are provided compounds having the structure **Q**:

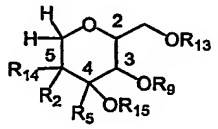


Q

wherein:

R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9, R_{13}, R_{15} are each independently hydrogen, alkylcarbonyl, substituted alkylcarbonyl, arylcarbonyl, and hydroxyl protecting group, R_{14} is cyano; R_{15} is hydrogen, trimethylsilyl, or tert-butyldimethylsilyl.

In yet another embodiment of the invention, there are provided compounds having the structure **Q**:



Q

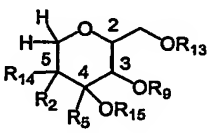
wherein:

R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9, R_{13} and R_{15} are each independently hydrogen, alkyl, substituted alkyl, aryl, alkylcarbonyl, substituted alkylcarbonyl, arylcarbonyl, trimethylsilyl, tert-butyldimethylsilyl, and hydroxyl protecting group; R_{14} is alkylthio, or arylthio

With the proviso that:

stereoisomer (2R,3R,4S,5R) and (2R,3R,4S,5S) cannot have $R_2 = R_5$ = hydrogen, $R_9 = R_{13} = R_{15}$ = acetyl, and R_{14} = ethylthio; stereoisomer (2R,3R,4S,5R) and (2R,3R,4S,5S) cannot have $R_2 = R_5$ = hydrogen, $R_9 = R_{13} = R_{15}$ = acetyl, and R_{14} = n-propylthio; stereoisomers (2R,3S,4S,5R) and (2R,3S,4S,5S) cannot have $R_2 = R_5 = R_9 = R_{13} = R_{15}$ = hydrogen and R_{14} = benzylthio; stereoisomers (2R,3R,4S,5R) and (2R,3R,4S,5S) cannot have $R_2 = R_5$ = hydrogen, $R_9 = R_{13} = R_{15}$ = acetyl, and R_{14} = benzylthio.

In yet another embodiment of the invention, there are provided compounds having the structure **Q**:



Q

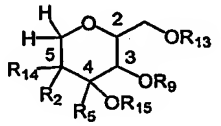
wherein:

R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9 is hydrogen, alkyl, substituted alkyl, aryl, alkylcarbonyl, substituted alkylcarbonyl, arylcarbonyl, trimethylsilyl, tert-butyldimethylsilyl, or hydroxyl protecting group; R_{13} is alkyl, substituted alkyl, aryl, alkylcarbonyl, substituted alkylcarbonyl, arylcarbonyl, trimethylsilyl, tert-butyldimethylsilyl, or hydroxyl protecting group; R_{14} is NHR_{18} where R_{18} is hydrogen, alkyl, substituted alkyl, aryl, alkylcarbonyl, substituted alkylcarbonyl, arylcarbonyl, or amino protecting group; R_{15} is hydrogen

With the proviso that:

stereoisomers (2R,3S,4R,5R) cannot have $R_2 = R_5 = R_9 = R_{15}$ = hydrogen, R_{13} = acetyl, and R_{14} = acetamido; stereoisomers (2R,3S,4S,5S) and (2R,3R,4R,5S) cannot have $R_2 = R_5 = R_9 = R_{15}$ = hydrogen, R_{13} = tert-butyltrimethylsilyl, and R_{14} = trichloroacetamido.

In yet another embodiment of the invention, there are provided compounds having the structure **Q**:



Q

wherein:

R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9 and R_{15} are each independently hydrogen, alkyl, substituted alkyl, aryl, alkylcarbonyl, substituted alkylcarbonyl, arylcarbonyl, trimethylsilyl, tert-butyldimethylsilyl, and hydroxyl protecting group; R_{13} is alkyl, substituted alkyl, aryl, alkylcarbonyl, substituted alkylcarbonyl, arylcarbonyl, trimethylsilyl, tert-butyldimethylsilyl, or hydroxyl protecting group; R_{14} is phthalimide, substituted phthalimide, maleimide substituted maleimide, or $NR_{18}R_{19}$ where R_{18} and R_{19} are each independently alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, heteroaryl, saturated heteroaryl, and amino protecting group, and R_{18} and R_{19} maybe taken together with the nitrogen to which

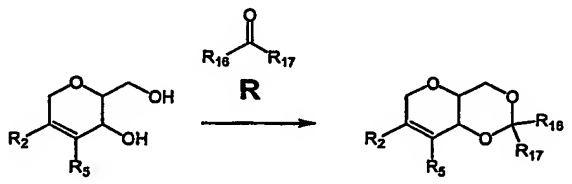
they are attached forming a cyclic system containing 3 to 10 carbon atoms with at least one substituent as defined for a substituted alkyl.

With the proviso that:

stereoisomer (2R,3R,4R,5S) cannot have $R_2 = R_5 =$ hydrogen, $R_9 = R_{13} = R_{15} =$ acetyl, and $R_{14} =$ phtalimido; stereoisomer (2R,3S,4R,5S) cannot have $R_2 = R_5 = R_9 = R_{13} = R_{15} =$ hydrogen, and $R_{14} =$ dimethylamino hydrogen chloride; stereoisomer (2R,3S,4R,5S) cannot have $R_2 = R_5 = R_9 = R_{13} = R_{15} =$ hydrogen, and $R_{14} =$ trimethylaminoiodide; and, stereoisomer (2R,3S,4R,5S) cannot have $R_2 = R_5 = R_9 = R_{13} = R_{15} =$ hydrogen, and $R_{14} =$ N,N-(benzyloxycarboxy)methylamino.

Invention compounds having structure **Q** maybe optically pure and include 6-(tert-butyldimethylsiloxymethyl)-5-hydroxy-4-(trimethylsiloxy)-tetrahydropyran-3-carbonitrile; 6-(tert-Butyldimethylsiloxymethyl)-5-hydroxy-4(-tert-butyldimethylsiloxy)-tetrahydropyran-3-carbonitrile; 6-(tert-butyldimethylsiloxymethyl)-5-hydroxy-4(-trimethylsiloxy)-tetrahydropyran-3-carbonitrile; 5-benzyloxy-2-hydroxymethyl-tetrahydropyran-3,4-diol; 5-benzylamino-2-(tert-butyldimethylsilanyloxymethyl)-tetrahydropyran-3,4-diol; 2-hydroxymethyl-tetrahydropyran-3,4,5-triol; 6-(tert-butyldimethylsilanyloxymethyl)-5-hydroxy-4-trimethylsilanyloxy-tetrahydro-pyran-3-carbonitrile; 2-(tert-butyldimethylsilanyloxymethyl)-tetrahydropyran-3,5-diol; 5-azido-2-(tert-butyldimethylsilanyloxymethyl)-tetrahydropyran-3,4-diol; 2-(tert-butyldimethylsilanyloxymethyl)-5-(3-methoxyphenylamino)-tetrahydropyran-3,4-diol; 2-hydroxymethyl-5-phenylsulfanyl-tetrahydropyran-3,4-diol

In one embodiment, the present invention provides a process for preparing a compound of formula **S**. Such a process can be performed, for example, by contacting a compound of formula **N** with a compound of formula **R** under conditions suitable to form a compound of formula **S**, as set forth below:



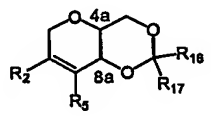
N **S**

In the scheme shown above, R_2, R_5, R_{16} and R_{17} are each independently hydrogen, alkyl, substituted alkyl, and aryl.

Solvents contemplated for use in the practice of this particular invention process are typically halogenated solvents, such as for example, dichloromethane, dichloroethane and the like, ethereal solvents, such as for example, diethyl ether, dioxane, tetrahydrofuran and the like, polar non-protic solvents, such as for example, acetonitrile and the like, aromatic solvents, such as for example, benzene, toluene, dichlorobenzene, xylene and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about 0°C up to about 150°C.

Compound **N** is typically contacted with compound **R** in the presence of an acidic reagent or a Lewis acidic reagent. Acidic reagents contemplated for use include, for example, formic acid, acetic acid, fumaric acid, phthalic acid, oxalic acid, pyridinium p-toluenesulfonate, p-toluenesulfonic acid, methanesulfonic acid, Montmorillonite Clay K-10, Montmorillonite Clay KSF, ammonium chloride, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, and the like. Lewis acidic reagents contemplated for use include, for example, boron trifluoride, trimethylsilyl chloride, trimethylsilylbromide, trimethylsilyl iodide, trimethylsilyl trifluoromethylsulfonate, cerium (III) chloride, scandium (III) trifluoromethanesulfonate, yttrium (III) trifluoromethanesulfonate, ytterbium (III) trifluoromethanesulfonate, lanthanum (III) trifluoromethanesulfonate, iron (III) chloride, zinc (II) chloride, zinc (II) bromide, zinc (II) iodide, zinc (II) trifluoromethanesulfonate, zinc (II) sulfate, magnesium sulfate, lithium perchlorate, copper (II) trifluoromethanesulfonate, copper (II) tetrafluoroborate.

In yet another embodiment of the invention, there are provided compounds having the structure **S**:



S

wherein:

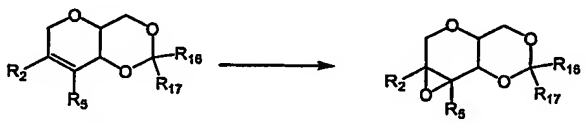
R_2, R_5, R_{16} and R_{17} are each independently hydrogen, alkyl, substituted alkyl, and aryl.

With the proviso that:

stereoisomer (4aR,8aS) cannot have $R_2 = R_5 = R_{16}$ = hydrogen and R_{17} = phenyl; and, stereoisomer (4aR,8aS) cannot have $R_2 = R_{16}$ = hydrogen, R_5 = (4-methoxyphenyl)-diphenylmethoxymethyl and R_{17} = phenyl

Invention compounds having structure **S** maybe optically pure and include 2,2-dimethyl-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine); (4aR,8aR)-2,2-dimethyl-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine; (4aS,8aS)-2,2-dimethyl-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine; (4aR,8aS)-2,2-dimethyl-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine; (4aS,8aR)-2,2-dimethyl-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine

In one embodiment, the present invention provides a process for preparing a compound of formula **T**. Such a process can be performed, for example, by contacting a compound of formula **S** under conditions suitable to form a compound of formula **T**, as set forth below:



S **T**

R_2, R_5, R_{16} and R_{17} are each independently hydrogen, alkyl, substituted alkyl, and aryl.

With the proviso that

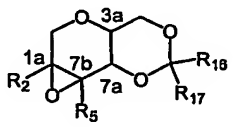
For compound of formula **S**, stereoisomer (3aR,7aS) cannot have $R_2 = R_5$ = hydrogen and $R_{16} = R_{17}$ = methyl

Solvents contemplated for use in the practice of this particular invention process are typically water, halogenated solvents, such as for example, dichloromethane, dichloroethane and the like, ethereal solvents, such as for example, diethyl ether, dioxane, tetrahydrofuran and the like, polar non-protic solvents, such as for example, acetonitrile, dimethyl formamide, dimethyl acetamide, N-methylpyrrolidine, dimethyl sulfoxide and the like, aromatic solvents, such as for example, benzene, toluene,

dichlorobenzene, xylene and the like, alcoholic solvents, such as for example, methanol, ethanol, isopropanol and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about -100°C up to about 100°C.

Compound **S** is typically contacted with an epoxidation reagent in the presence or absence of a transition metal reagent, and in the presence or absence of a ligand. Epoxidation reagents contemplated for use include, for example, oxygen, tert-butyl hydroperoxide, meta-chloroperbenzoic acid, dimethyl dioxirane, oxone, sodium hypochlorite, sodium periodate, iodosylbenzene and the like. Transition metal reagents contemplated for use include, for example, titanium tetraisopropoxide, polymer supported cyclopentadienyl titanium trichloride, zirconium tetraethoxide, hafnium tetraisopropoxide, vanadium pentoxide, niobium pentaethoxide, tantalum pentaisopropoxide, manganese (II) trifluoromethanesulfonate, iron (III) acetylacetonate, molybdenum hexacarbonyl, ruthenium dichloride tris(triphenylphosphine), cobalt (II) trifluoromethanesulfonate, and the like. Ligands contemplated for use include, for example, (R,R) diethyl tartarate, (S,S) diethyl tartarate, N-ethyl ephedrine, N-methylprolinol, porphyrin, 2,2'-[[(1S,2S)-1,2-diphenyl-1,2-ethanediyl]-bis(nitrilomethylidyne)]bis[6-(1,1-dimethylethyl)-4-methyl-phenol, 2,2'-[[(1R,2R)-1,2-diphenyl-1,2-ethanediyl]-bis(nitrilomethylidyne)]bis[6-(1,1-dimethylethyl)-4-methyl-phenol, 2,2'-[(1R,2R)-1,2-cyclohexanediylbis[(E)-nitrilomethylidyne]]bis[6-(1,1-dimethylethyl)-4-methyl-phenol and the like.

In yet another embodiment of the invention, there are provided compounds having the structure **T**:



T

wherein:

R_2, R_5, R_{16} and R_{17} are each independently hydrogen, alkyl, substituted alkyl, and aryl;

With the proviso that:

stereoisomer (1aR,3aR,7aR,7bR) cannot have R_2 = R_5 = R_{16} = hydrogen and R_{17} = phenyl; stereoisomer (1aS,3aR,7aR,7bS) cannot have R_2 = R_5 = R_{16} = hydrogen and R_{17} = phenyl; and, stereoisomer (1aR,3aS,7aS,7bR) cannot have R_2 = R_5 = R_{16} = hydrogen and R_{17} = phenyl.

In one embodiment, the present invention provides a process for preparing a compound of formula **U**. Such a process can be performed, for example, by contacting a compound of formula **T** with a nucleophile under conditions suitable to form a compound of formula **U**, as set forth below:

T **U**

R_2, R_5, R_{16} and R_{17} are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_{14} is hydrogen, halogen, alkyl, substituted alkyl, aryl, heteroaryl, saturated heteroaryl, cyano, azido, amino, alkylamino, arylamino, hydrazine, alkylhydrazino, arylhydrazino, alkylcarbonylhydrazino, arylcarbonylhydrazino, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, alkylcarboxy, arylcarboxy, N-protected amino acid, O-protected amino acid, or a solid support; R_{15} is hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, or hydroxyl protecting group.

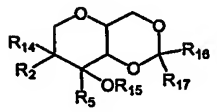
With the proviso that:

For compounds of formula **T**, stereoisomer (1aS,3aR,7aR,7bS) cannot have R_2 = R_5 = R_{16} = hydrogen and R_{17} = phenyl

Solvents contemplated for use in the practice of this particular invention process are typically water, halogenated solvents, such as for example, dichloromethane, dichloroethane and the like, ethereal solvents, such as for example, diethyl ether, dioxane, tetrahydrofuran and the like, polar non-protic solvents, such as for example, acetonitrile, dimethyl formamide, dimethyl acetamide, N-methylpyrrolidine, dimethyl sulfoxide and the like, aromatic solvents, such as for example, benzene, toluene, dichlorobenzene, xylene and the like, alcoholic solvents, such as for example, methanol, ethanol, isopropanol and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about 0°C up to about 150°C.

Compound **T** is typically contacted with a nucleophile in the presence or absence of a Lewis acidic reagent. Nucleophiles contemplated for use include, for example, water, potassium cyanide, trimethylsilyl cyanide, sodium azide, potassium iodide, sodium fluoride, potasslum hydroxide, methanol, sodium ethoxide, benzyl alcohol, 3,5-dimethylphenol, sodium phenoxide, ethyl thiol, potassium phenyl thiolate, ammonia, ammonium hydroxide, hydrazine, ethyl hydrazine, phenyl hydrazine, benzoylhydrazine, methylamine, benzylamine, dibutylamine, aniline, 3-methoxyaniline, diphenylamine, sodium amide, Lithium dimethylamide, potassium benzylmethylamide, lithium anilide, hydrazine, potassium hydrizide, methylhydrazine, phenylhydrazine, benzoylhydrazine, acetylhydrazine, piperidine, morpholine, piperazine, thiomorpholine, pyrrolidine, lithium piperidide, potassium morpholinide, phthalimide, maleimide, adenine, guanine, uracil, thymine, cytosine, imidazole, pyrrole, indole, tetrazole, glycine methyl ester, serine tert-butyl ester, valine ethyl ester lithium salt, N-benzylleucine, methyl lithium, ethyl magnesium bromide, phenyl lithium, diethyl zinc, diethyl mercury, trimethyl aluminum, triethyl indium, trimethyl gallium, Merrifield resin, Wang resin, Rink resin, Wang resin lithium salt, compound of formula **N** and the like. Lewis acidic reagents contemplated for use include, for example, boron trifluoride, boron trifluoride etherate, boron trifluoride tetrahydrofuran complex, boron trifluoride tert-butyl-methyl ether complex, boron trifluoride dibutyl ether complex, boron trifluoride dihydrate, boron trifluoride di-acetic acid complex, boron trifluoride dimethyl sulfide complex, boron trichloride, boron trichloride dimethyl sulfide complex, boron tribromide, boron tribromide dimethyl sulfide complex, boron triiodide, trimethoxyborane, triethoxyborane, trimethylaluminum, triethylaluminum, aluminum trichloride, aluminum trichloride tetrahydrofuran complex, aluminum tribromide, titanium tetrachloride, titanium tetrabromide, titanium iodide, titanium tetraethoxide, titanium tetraisopropoxide, scandium (III) trifluoromethanesulfonate, yttrium (III) trifluoromethanesulfonate, ytterbium (III) trifluoromethanesulfonate, lanthanum (III) trifluoromethanesulfonate, zinc (II) chloride, zinc (II) bromide, zinc (II) iodide, zinc (II) trifluoromethanesulfonate, zinc (II) sulfate, magnesium sulfate, lithium perchlorate, copper (II) trifluoromethanesulfonate, copper (II) tetrafluoroborate and the like.

In yet another embodiment of the invention, there are provided compounds having the structure **U**:



U

wherein:

R_2, R_5, R_{16} and R_{17} are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_{14} is hydrogen, halogen, alkyl, substituted alkyl, aryl, heteroaryl, saturated heteroaryl, cyano, azido, amino, alkylamino, arylamino, hydrazine, alkylhydrazino, arylhydrazino, alkylcarbonylhydrazino, arylcarbonylhydrazino, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, alkylcarboxy, arylcarboxy, N-protected amino acid, O-protected amino acid, or a solid support; and R_{15} is hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, or hydroxyl protecting group.

With the proviso that

if R_{16} is methyl then R_{17} cannot be methyl; if R_{16} is hydrogen then R_{17} cannot be phenyl; if $R_2 = R_5 = R_{15} = R_{16}$ = hydrogen and R_{14} = hydroxy then R_{17} cannot be 3-nitrophenyl; if $R_2 = R_5 = R_{14} = R_{15} = R_{16}$ = hydrogen then R_{17} cannot be 4-nitrophenyl; if $R_2 = R_5 = R_{14} = R_{15} = R_{16}$ = hydrogen then R_{17} cannot be 4-methoxyphenyl; if $R_2 = R_5 = R_{16}$ = hydrogen and R_{14} = methoxy and R_{15} = methyl then R_{17} cannot be 4-methoxyphenyl; and, if $R_2 = R_5 = R_{15} = R_{16}$ = hydrogen and R_{14} = hydroxy then R_{17} cannot be 4-methoxyphenyl.

In one embodiment, the present invention provides a process for preparing a compound of formula **V**. Such a process can be performed, for example, by contacting a compound of formula **S** under conditions suitable to form a compound of formula **V**, as set forth below:

S **V**

In the scheme shown above, R_2, R_5, R_{16} and R_{17} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, and aryl; R_{10} and R_{11} are hydrogen

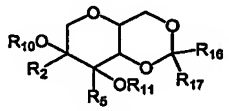
With the proviso that:

stereoisomer (4aR,8aS) cannot have R_{16} = hydrogen and R_{17} = phenyl

Solvents contemplated for use in the practice of this particular invention process are typically water, halogenated solvents, such as dichloromethane and the like, alcoholic solvents, such as for example 2-methyl-2-propanol and the like, ethereal solvents, such as for example tetrahydrofuran and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about -78°C up to about 60°C.

Compound **S** is typically contacted with a suitable mixture of an oxidant, a co-oxidant and a ligand. Oxidants contemplated for use include, for example, osmium tetroxide, potassium permanganate, thallium acetate, potassium periodate, silver acetate and the like, co-oxidants contemplated for use include, for example, N-methylmorpholine oxide, trimethylamine oxide, tert-butyl peroxide, iodine, potassium ferricyanide and the like, ligands contemplated for use include, for example, pyridine, quinuclidine, dihydroquinine acetate, dihydroquinidine acetate, dihydroquinine anthraquinone-1,4-diyl diether ($(DHQ)_2AQN$), dihydroquinine phthalazine-1,4-diyl diether ($(DHQ)_2PHAL$), dihydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether ($(DHQ)_2PYR$), dihydroquinidine anthraquinone-1,4-diyl diether ($(DHQD)_2AQN$), dihydroquinidine phthalazine-1,4-diyl diether ($(DHQD)_2PHAL$), dihydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether ($(DHQD)_2PYR$), tetraethyl ammonium hydroxide, tetraethyl ammonium acetate, N,N,N'N'-tetramethylethylene diamine (TMEDA) and the like.

In yet another embodiment of the invention, there are provided compounds having the structure **V**:



V

wherein:

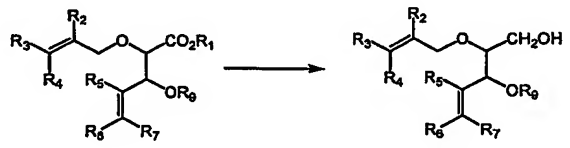
R_2, R_5, R_{16} and R_{17} are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_{10} and R_{11} are each independently hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, and hydroxyl protecting group;

With the proviso that:

If R_{16} is methyl then R_{17} cannot be methyl; if R_{16} is hydrogen then R_{17} cannot be phenyl; if $R_2 = R_5 = R_{10} = R_{11} = R_{16}$ = hydrogen then R_{17} cannot be 3-nitrophenyl; if $R_2 = R_5 = R_{16}$ = hydrogen and R_{14} = hydroxy then R_{17} cannot be 4-methoxyphenyl; and, if $R_2 = R_5 = R_{16}$ = hydrogen and $R_{10} = R_{11}$ = methyl then R_{17} cannot be 4-methoxyphenyl.

Invention compounds having structure **V** maybe optically pure and include 2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol; (4aS,7R,8R,8aR)-2,2-dimethyl-hexahydropyrano[3,2-d][1,3]dioxine-7,8-diol; (4aS,7S,8S,8aR)-2,2-dimethyl-hexahydropyrano[3,2-d][1,3]dioxine-7,8-diol; (4aR,7R,8R,8aS)-2,2-dimethyl-hexahydropyrano[3,2-d][1,3]dioxine-7,8-diol; (4aS,7R,8R,8aS)-2,2-dimethyl-hexahydropyrano[3,2-d][1,3]dioxine-7,8-diol; (4aR,7S,8S,8aR)-2,2-dimethyl-hexahydropyrano[3,2-d][1,3]dioxine-7,8-diol; (4aS,7S,8S,8aS)-2,2-dimethyl-hexahydropyrano[3,2-d][1,3]dioxine-7,8-diol; and, (4aR,7R,8R,8aR)-2,2-dimethyl-hexahydropyrano[3,2-d][1,3]dioxine-7,8-diol

In one embodiment, the present invention provides a process for preparing a compound of formula **W**. Such a process can be performed, for example, by contacting a compound of formula **G** under conditions suitable to form a compound of formula **W**, as set forth below:



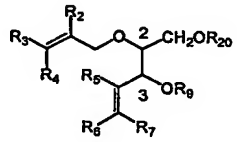
G **W**

In the scheme shown above, R_1 is typically alkyl, substituted alkyl, or aryl; R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_3, R_4, R_6, R_7 are either all hydrogen or, of R_3, R_4, R_6, R_7 three are hydrogen and the fourth is alkyl, substituted alkyl, or aryl; R_9 is hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, or hydroxyl protecting group. In another embodiment, R_1 is ethyl, R_2-R_7 and R_9 are hydrogen.

Solvents contemplated for use in the practice of this particular invention process are typically water, ammonia, ethereal solvents, such as for example, diethyl ether, dioxane, tetrahydrofuran and the like, alcoholic solvents, such as for example, methanol, ethanol, isopropanol, 1,2-ethanediol, polyethylene glycol and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about -100°C up to about 100°C.

Compound **G** is typically contacted with a reducing reagent in the presence or absence of an acidic reagent or a Lewis acidic reagent. Reducing reagents contemplated for use include, for example, borane-dimethyl sulfide complex, 9-borabicyclo[3.3.1.]nonane (9-BBN), catechol borane, lithium borohydride, sodium borohydride, sodium borohydride-methanol complex, potassium borohydride, sodium hydroxyborohydride, lithium triethylborohydride, lithium n-butylborohydride, sodium cyanoborohydride, calcium (II) borohydride, lithium aluminum hydride, diisobutylaluminum hydride, n-butyl-diisobutylaluminum hydride, sodium bis-methoxyethoxyaluminum hydride, triethoxysilane, diethoxymethylsilane, lithium hydride, lithium, sodium, hydrogen Ni/B, and the like. Acidic reagents contemplated for use include, for example, acetic acid, methanesulfonic acid, hydrochloric acid, and the like. Lewis acidic reagents contemplated for use include, for example, trimethoxyborane, triethoxyborane, aluminum trichloride, lithium chloride, vanadium trichloride, dicyclopentadienyl titanium dichloride, cesium fluoride, potassium fluoride, zinc (II) chloride, zinc (II) bromide, zinc (II) iodide, and the like.

In yet another embodiment of the invention, there are provided compounds having the structure **W**:



W

wherein:

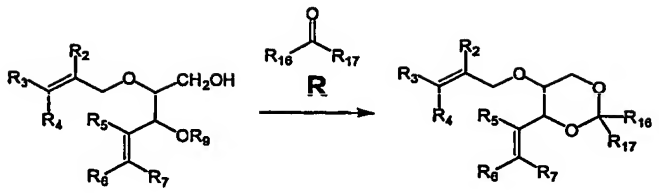
R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_3, R_4, R_6, R_7 are either all hydrogen or, of R_3, R_4, R_6, R_7 three are hydrogen and the fourth is alkyl, substituted alkyl, or aryl; R_9 and R_{20} are each independently hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, and hydroxyl protecting group

With the proviso that:

stereoisomer (2R,3R) cannot have $R_3 = R_4 = R_6 = R_7 = R_9 = R_{20}$ = hydrogen; stereoisomer (2R,3R) cannot have $R_3 = R_4 = R_6 = R_7$ = hydrogen and $R_9 = R_{20}$ = benzoyl; stereoisomer (2R,3R) cannot have $R_3 = R_4 = R_7 = R_9 = R_{20}$ = hydrogen and R_6 = methyl; stereoisomer (2R,3R) cannot have $R_3 = R_4 = R_7$ = hydrogen and R_6 = methyl and $R_9 = R_{20}$ = benzoyl; and, if R_{20} = benzyl then R_3, R_4, R_6, R_7, R_9 cannot be hydrogen

Invention compounds having structure **W** maybe optically pure and include 2-allyloxy-pent-4-ene-1,3-diol, (2S,3S)-2-allyloxy-pent-4-ene-1,3-diol; (2R,3S)-2-allyloxy-pent-4-ene-1,3-diol; (2S,3R)-2-allyloxy-pent-4-ene-1,3-diol.

In one embodiment, the present invention provides a process for preparing a compound of formula **X**. Such a process can be performed, for example, by contacting a compound of formula **W** with a compound of formula **R** under conditions suitable to form a compound of formula **X**, as set forth below:



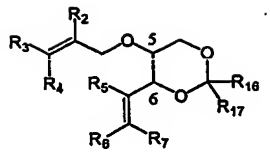
W X

In the scheme shown above, R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_3, R_4, R_6, R_7 are either all hydrogen or, of R_3, R_4, R_6, R_7 three are hydrogen and the fourth is alkyl, substituted alkyl, or aryl; R_{16} and R_{17} are each independently hydrogen, alkyl, substituted alkyl, and aryl.

Solvents contemplated for use in the practice of this particular invention process are typically halogenated solvents, such as for example, dichloromethane, dichloroethane and the like, ethereal solvents, such as for example, diethyl ether, dioxane, tetrahydrofuran and the like, polar non-protic solvents, such as for example, acetonitrile and the like, aromatic solvents, such as for example, benzene, toluene, dichlorobenzene, xylene and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about 0°C up to about 150°C.

Compound **W** is typically contacted with compound **R** in the presence of an acidic reagent or a Lewis acidic reagent. Acidic reagents contemplated for use include, for example, formic acid, acetic acid, fumaric acid, phthalic acid, oxalic acid, pyridinium p-toluenesulfonate, p-toluenesulfonic acid, methanesulfonic acid, Montmorillonite Clay K-10, Montmorillonite Clay KSF, ammonium chloride, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, and the like. Lewis acidic reagents contemplated for use include, for example, boron trifluoride, trimethylsilyl chloride, trimethylsilylbromide, trimethylsilyl iodide, trimethylsilyl trifluoromethylsulfonate, cerium (III) chloride, scandium (III) trifluoromethanesulfonate, yttrium (III) trifluoromethanesulfonate, ytterbium (III) trifluoromethanesulfonate, lanthanum (III) trifluoromethanesulfonate, iron (III) chloride, zinc (II) chloride, zinc (II) bromide, zinc (II) iodide, zinc (II) trifluoromethanesulfonate, zinc (II) sulfate, magnesium sulfate, lithium perchlorate, copper (II) trifluoromethanesulfonate, copper (II) tetrafluoroborate.

In yet another embodiment of the invention, there are provided compounds having the structure **X**:



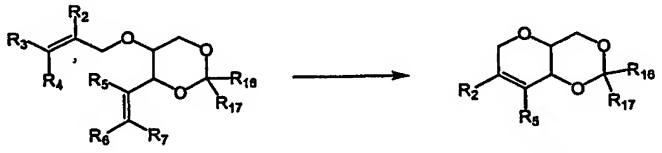
X

wherein:

R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_3, R_4, R_6, R_7 are either all hydrogen or, of R_3, R_4, R_6, R_7 three are hydrogen and the fourth is alkyl, substituted alkyl, and aryl; R_{16} and R_{17} are each independently hydrogen, alkyl, substituted alkyl, and aryl

Invention compounds having structure **X** maybe optically pure and include 5-allyloxy-2,2-dimethyl-4-vinyl-[1,3]dioxane; (5R,6R)-5-allyloxy-2,2-dimethyl-4-vinyl-[1,3]dioxane; (5S,6S)-5-allyloxy-2,2-dimethyl-4-vinyl-[1,3]dioxane; (5S,6R)-5-allyloxy-2,2-dimethyl-4-vinyl-[1,3]dioxane; (5R,6S)-5-allyloxy-2,2-dimethyl-4-vinyl-[1,3]dioxane.

In one embodiment, the present invention provides a process for preparing a compound of formula **S**. Such a process can be performed, for example, by contacting a compound of formula **X** under conditions suitable to form a compound of formula **S**, as set forth below:



X S

In the scheme shown above, R_2, R_5, R_{16} and R_{17} are each independently hydrogen, alkyl, substituted alkyl, and aryl. In another embodiment, R_2-R_7 are hydrogen and R_{16} and R_{17} are methyl; In still another embodiment, R_2, R_3, R_4, R_5, R_7 are hydrogen, and R_6, R_{16}, R_{17} are methyl; In yet another embodiment, R_2, R_3, R_4, R_5, R_7 are hydrogen, R_6 is phenyl, and R_{16}-R_{17} are methyl.

In one embodiment, the present invention provides a process for preparing compound of formula **S** as a mixture of stereoisomers, such as for example, cis or trans

stereoisomers and the like. In another embodiment, the invention provides a process for separating such stereoisomers, such as for example, chromatography, crystallization, re-crystallization, distillation and the like. In still another embodiment, the invention provides a process for preparing compound **S** as an optically pure isomer.

Solvents contemplated for use in the practice of this particular invention process are typically water, halogenated solvents, such as for example, dichloromethane, dichloroethane and the like, ethereal solvents, such as for example, diethyl ether, dioxane, tetrahydrofuran and the like, polar non-protic solvents, such as for example, acetonitrile, dimethyl formamide, dimethyl acetamide, N-methylpyrrolidine, dimethyl sulfoxide and the like, aromatic solvents, such as for example, benzene, toluene, dichlorobenzene, xylene and the like, alcoholic solvents, such as for example, methanol, ethanol, isopropanol and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about 0°C up to about 150°C.

Compound **X** is typically contacted with a ring-closing metathesis catalyst. Ring-closing metathesis catalysts contemplated for use include, for example, 2,6-diisopropylphenylimidoneophylidene molybdenum (IV) bis-(tert-butoxide), 2,6-diisopropylphenylimidoneophylidene molybdenum (IV) bis-(hexafluoro-tert-butoxide), 2,6-diisopropylphenylimidoneophylidene[racemic-BIPHEN] molybdenum (IV), 2,6-diisopropylphenylimidoneophylidene[(R)-(+)-BIPHEN] molybdenum (IV), 2,6-diisopropylphenylimidoneophylidene[(S)-(-)-BIPHEN] molybdenum (IV), bis-(tricyclohexylphosphine)benzylidine ruthenium (IV) dichloride, bis-(tricyclohexylphosphine)-3-methyl-2-butenylidene ruthenium (IV) dichloride, bis-(tricyclopentylphosphine)benzylidine ruthenium (IV) dichloride, bis-(tricyclopentylphosphine)-3-methyl-2-butenylidene ruthenium (IV) dichloride, tricyclohexylphosphine-(1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene)-benzylidine ruthenium (IV) dichloride, tricyclohexylphosphine-(1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene)-benzylidine ruthenium (IV) dichloride, (1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene)-2-isopropoxyphenylmethylene ruthenium (IV) dichloride, (tricyclopentylphosphine)-2-isopropoxyphenylmethylene ruthenium (IV) dichloride, (tricyclopentylphosphine)-2-methoxy-3-naphthylmethylene ruthenium (IV) dichloride and the like.

In one embodiment, the present invention provides a process for preparing a compound of formula **P**. Such a process can be performed, for example, by contacting a compound of formula **Y** under conditions suitable to form a compound of formula **P**, as set forth below:

Y **P**

In the scheme shown above, R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9 and R_{13} are each independently hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, and hydroxyl protecting group.

Solvents contemplated for use in the practice of this particular invention process are typically water, halogenated solvents, such as for example, dichloromethane, dichloroethane and the like, ethereal solvents, such as for example, diethyl ether, dioxane, tetrahydrofuran and the like, polar non-protic solvents, such as for example, acetonitrile, dimethyl formamide, dimethyl acetamide, N-methylpyrrolidine, dimethyl sulfoxide and the like, aromatic solvents, such as for example, benzene, toluene, dichlorobenzene, xylene and the like, alcoholic solvents, such as for example, methanol, ethanol, isopropanol and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about 0°C up to about 40°C.

Compound **Y** is typically contacted with a resolving enzyme in the presence of an acylating agent. Resolving enzymes contemplated for use include lipase, esterase, peptidase, acylase or protease enzymes of mammalian, plant, fungal or bacterial origin, such as for example, Lipase Amano lipase PS-D (immobilized lipase from *Pseudomonas cepacia*), Amano Lipase PS-C (immobilized lipase from *Pseudomonas cepacia*), Roche Chirazyme L-3 (lipase, lyophilizate, from *Candida Rugosa)*, Roche Chirazyme L-3 (purified lipase, lyophilizate, from *Candida Rugosa*), Roche Chirazyme L-3 (purified lipase, carrier-fixed, carrier 2, lyophilizate, from *Candida rugosa*), Roche Chirazyme L-5 (lipase, solution, from *Candida antartica, type A)*, Roche Chirazyme L-5 (lipase, lyophilizate, from *Candida antartica, type A*), Roche Chirazyme L-5 (lipase, carrier-fixed,

carrier 1, lyophilizate, from *Candida antartica, type A)*, Roche Chirazyme L-10 (lipase, lyophilizate, from *Alcaligenes sp.*), Altus Biologics 8 (lipase from *Mucor miehei*) and Altus Biologics 27 (lipase from *Alcaligenes sp.*) and the like. Acylating agents contemplated for use include, for example, ethyl acetate, vinyl acetate, vinyl propionate, vinyl butyrate, isopropenyl acetate, 1-ethoxyvinyl acetate, trichloroethyl butyrate, trifluoroethyl butyrate, trifluoroethyl laureate, S-ethyl thiooctanoate, biacetyl monooxime acetate, acetic anhydride, succinic anhydride, amino acid, diketene and the like.

Compound **Y** can also be contacted with an electrophilic reagent. Electrophilic reagents contemplated for use include, for example, diazomethane, trimethylsilyldiazomethane, alkyl halides, such as for example methyl iodide, benzyl bromide and the like, alkyl triflates, such as for example methyl triflate and the like, alkyl sulfonates, such as for example ethyl toluenesulfonate, butyl methanesulfonate and the like, acyl halides, such as for example acetyl chloride, benzoyl bromide and the like, acid anhydrides, such as for example acetic anhydride, succininc anhydride, maleic anhydride and the like, isocyanates, such as for example methyl isocyanate, phenylisocyanate and the like, chloroformates, such as for example methyl chloroformate, ethyl chloroformate, benzyl chloroformate and the like, sulfonyl halides, such as for example methanesulfonyl chloride, p-tolunesulfonyl chloride and the like, silyl halides, such as for example trimethylsilyl chloride, tertbutyldimethyl silyll chloride and the like, phosphoryl halide such as for example dimethyl chlorophosphate and the like, alpha-beta-unsaturated carbonyl such as for example acrolein, methyl vinyl ketone, cinnamaldehyde and the like.

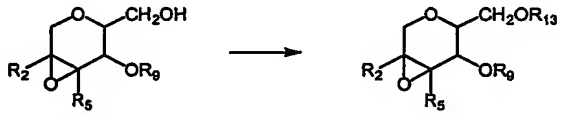
Compound **Y** can also be contacted with an alcohol in the presence of an azodicarboxylate and a phosphine base, or any suitable mixtures thereof. Azodicarboxylates contemplated for use include, for example, diethyl azodicarboxylate, dicyclohexyl azodicarboxylate, diisopropyl azodicarboxylate and the like. Phosphine bases contemplated for use include, for example, triethylphosphine, tricyclopentylphosphine, tricyclohexylphosphine, triphenylphosphine, tri-o-tolylphosphine, and the like.

Compound **Y** can also be contacted with a carboxylic acid or an amino acid in the presence of a coupling agent and a base, or any suitable mixtures thereof. Coupling agents contemplated for use include, for example, dicyclohexylcarbodiimide (DCC),

diisopropyl carbodiiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDCI), N-hydroxybenzotriazole (HOBT), N-hydroxysuccinimide (HOSu), 4-nitrophenol, pentafluorophenol, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), O-benzotriazole-N,N,N'N'-tetramethyluronium hexafluorophosphate (HBTU), benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP), benzotriazole-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate, bromo-trispyrrolidino- phosphonium hexafluorophosphate, 2-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU), O-(N-succinimidyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TSTU), tetramethylfluoroformamidinium hexafluorophosphate and the like. Bases contemplated for use include, for example, triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine, and the like.

In another embodiment, the invention provides a process for separating compound of formula **P**, such as for example, chromatography, crystallization, re-crystallization, distillation and the like.

In one embodiment, the present invention provides a process for preparing a compound of formula **P**. Such a process can be performed, for example, by contacting a compound of formula **Z** under conditions suitable to form a compound of formula **P**, as set forth below:



Z **P**

In the scheme shown above, R_2 and R_5 are each independently hydrogen, alkyl, substituted alkyl, and aryl; R_9 and R_{13} are each independently hydrogen, alkyl, substituted alkyl, alkylcarbonyl, substituted alkylcarbonyl, aryl, arylcarbonyl, and hydroxyl protecting group.

Solvents contemplated for use in the practice of this particular invention process are typically water, halogenated solvents, such as for example, dichloromethane, dichloroethane and the like, ethereal solvents, such as for example, diethyl ether, dioxane, tetrahydrofuran and the like, polar non-protic solvents, such as for example,

acetonitrile, dimethyl formamide, dimethyl acetamide, N-methylpyrrolidine, dimethyl sulfoxide and the like, aromatic solvents, such as for example, benzene, toluene, dichlorobenzene, xylene and the like, alcoholic solvents, such as for example, methanol, ethanol, isopropanol and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about 0°C up to about 40°C.

Compound **Z** is typically contacted with a resolving enzyme in the presence of an acylating agent. Resolving enzymes contemplated for use include lipase, esterase, peptidase, acylase or protease enzymes of mammalian, plant, fungal or bacterial origin, such as for example, Lipase Amano lipase PS-D (immobilized lipase from *Pseudomonas cepacia*), Amano Lipase PS-C (immobilized lipase from *Pseudomonas cepacia*), Roche Chirazyme L-3 (lipase, lyophilizate, from *Candida Rugosa)*, Roche Chirazyme L-3 (purified lipase, lyophilizate, from *Candida Rugosa*), Roche Chirazyme L-3 (purified lipase, carrier-fixed, carrier 2, lyophilizate, from *Candida rugosa*), Roche Chirazyme L-5 (lipase, solution, from *Candida antartica, type A)*, Roche Chirazyme L-5 (lipase, lyophilizate, from *Candida antartica, type A*), Roche Chirazyme L-5 (lipase, carrier-fixed, carrier 1, lyophilizate, from *Candida antartica, type A)*, Roche Chirazyme L-10 (lipase, lyophilizate, from *Alcaligenes sp.*), Altus Biologics 8 (lipase from *Mucor miehei*) and Altus Biologics 27 (lipase from *Alcaligenes sp.*) and the like. Acylating agents contemplated for use include, for example, ethyl acetate, vinyl acetate, vinyl propionate, vinyl butyrate, isopropenyl acetate, 1-ethoxyvinyl acetate, trichloroethyl butyrate, trifluoroethyl butyrate, trifluoroethyl laureate, S-ethyl thiooctanoate, biacetyl monooxime acetate, acetic anhydride, succinic anhydride, amino acid, diketene and the like.

Compound **Z** can also be contacted with an electrophilic reagent. Electrophilic reagents contemplated for use include, for example, diazomethane, trimethylsilyldiazomethane, alkyl halides, such as for example methyl iodide, benzyl bromide and the like, alkyl triflates, such as for example methyl triflate and the like, alkyl sulfonates, such as for example ethyl toluenesulfonate, butyl methanesulfonate and the like, acyl halides, such as for example acetyl chloride, benzoyl bromide and the like, acid anhydrides, such as for example acetic anhydride, succininc anhydride, maleic anhydride and the like, isocyanates, such as for example methyl isocyanate, phenylisocyanate and the like, chloroformates, such as for example methyl chloroformate, ethyl chloroformate, benzyl chloroformate and the like, sulfonyl halides, such as for example methanesulfonyl chloride, p-tolunesulfonyl chloride and the like, silyl

halides, such as for example trimethylsilyl chloride, tertbutyldimethyl silyll chloride and the like, phosphoryl halide such as for example dimethyl chlorophosphate and the like, alpha-beta-unsaturated carbonyl such as for example acrolein, methyl vinyl ketone, cinnamaldehyde and the like.

Compound **Z** can also be contacted with an alcohol in the presence of an azodicarboxylate and a phosphine base, or any suitable mixtures thereof. Azodicarboxylates contemplated for use include, for example, diethyl azodicarboxylate, dicyclohexyl azodicarboxylate, diisopropyl azodicarboxylate and the like. Phosphine bases contemplated for use include, for example, triethylphosphine, tricyclopentylphosphine, tricyclohexylphosphine, triphenylphosphine, tri-o-tolylphosphine, and the like.

Compound **Z** can also be contacted with a carboxylic acid or an amino acid in the presence of a coupling agent and a base, or any suitable mixtures thereof. Coupling agents contemplated for use include, for example, dicyclohexylcarbodiimide (DCC), diisopropyl carbodiiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDCI), N-hydroxybenzotriazole (HOBT), N-hydroxysuccinimide (HOSu), 4-nitrophenol, pentafluorophenol, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), O-benzotriazole-N,N,N'N'-tetramethyluronium hexafluorophosphate (HBTU), benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP), benzotriazole-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate, bromo-trispyrrolidino- phosphonium hexafluorophosphate, 2-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU), O-(N-succinimidyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TSTU), tetramethylfluoroformamidinium hexafluorophosphate and the like. Bases contemplated for use include, for example, triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine, and the like.

In another embodiment, the invention provides a process for separating compound of formula **P**, such as for example, chromatography, crystallization, re-crystallization, distillation and the like.

General Methods of Preparation

Used herein, the following abbreviations have the following meanings: Me refers to methyl (CH_3-), Et refers to ethyl (CH_3CH_2-), i-Pr refers to isopropyl ($(CH_3)_2CH_2$-), t-Bu or tert-butyl refers to tertiary butyl ($(CH_3)_3CH$-), Ph refers to phenyl, Bn refers to benzyl ($PhCH_2$-), Bz refers to benzoyl (PhCO-), MOM refers to methoxymethyl, Ac refers to acetyl, TMS refers to trimethylsilyl, TBS refers to ter-butyldimethylsilyl, Ms refers to methanesulfonyl (CH_3SO_2-), Ts refers to p-toluenesulfonyl (p-CH_3PhSO_2-), Tf refers to trifluoromethanesulfonyl (CF_3SO_2-), TfO refers to trifluoromethanesulfonate (CF_3SO_3-), DMF refers to N,N-dimethylformamide, DCM refers to dichloromethane (CH_2Cl_2), THF refers to tetrahydrofuran, EtOAc refers to ethyl acetate, Et_2O refers to diethyl ether, MeCN refers to acetonitrile (CH_3CN), NMP refers to 1-N-methyl-2-pyrrolidinone, DMA refers to N,N-dimethylacetamide, DMSO refers to dimethylsulfoxide, DCC refers to 1,3-dicyclohexyldicarbodiimide, EDCI refers to 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, Boc refers to tert-butylcarbonyl, Fmoc refers to 9-fluorenylmethoxycarbonyl, TBAF refers to tetrabutylammonium fluoride, TBAI refers to tetrabutylammonium iodide, TMEDA refers to N,N,N,N-tetramethylethylene diamine, Dess-Martin periodinane or Dess Martin reagent refers to 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one, DMAP refers to 4-N,N-dimethylaminopyridine, $(i\text{-}Pr)_2NEt$ or DIEA or Hunig's base refers to N,N-diethylisopropylamine, DBU refers to 1,8-Diazabicyclo[5.4.0]undec-7-ene, $(DHQ)_2AQN$ refers to dihydroquinine anthraquinone-1,4-diyl diether, $(DHQ)_2PHAL$ refers to dihydroquinine phthalazine-1,4-diyl diether, $(DHQ)_2PYR$ refers to dihydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether, $(DHQD)_2AQN$ refers to dihydroquinidine anthraquinone-1,4-diyl diether, $(DHQD)_2PHAL$ refers to dihydroquinidine phthalazine-1,4-diyl diether, $(DHQD)_2PYR$ refers to dihydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether, LDA refers to lithium diisopropylamide, LiTMP refers to lithium 2,2,6,6-tetramethylpiperdinamide, n-BuLi refers to n-butyllithium, t-BuLi refers to tert-butyl lithium, IBA refers to 1-hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide, OsO_4 refers to osmium tetroxide, m-CPBA refers to meta-chloroperbenzoic acid, DMD refers to dimethyl dioxirane, PDC refers to pyridinium dichromate, NMO refers to N-methyl morpholine-N-oxide, NaHMDS refers to sodium hexamethyldisilazide, LiHMDS refers to lithium hexamethyldisilazide, HMPA refers to hexamethylphosphoramide, TMSCl refers to trimethylsilyl chloride, TMSCN refers to trimethylsilyl cyanide, TBSCl refers to tert-butyldimethylsilyl chloride, TFA refers to

trifluoroacetic acid, TFAA refers to trifluoroacetic anhydride, AcOH refers to acetic acid, Ac_2O refers to acetic anhydride, AcCl refers to acetyl chloride, TsOH refers to p-toluenesulfonic acid, TsCl refers to p-toluenesulfonyl chloride, MBHA refers to 4-methylbenzhydrylamine, BHA refers to benzhydrylamine, $ZnCl_2$ refers to zinc (II) dichloride, BF_3 refers to boron trifluoride, $Y(OTf)_2$ refers to yttrium (III) trifluoromethanesulfonate, $Cu(BF_4)_2$ refers to copper (II) tetrafluoroborate, LAH refers to lithium aluminum hydride ($LiAlH_4$), $NaHCO_3$ refers to sodium bicarbonate, K_2CO_3 refers to potassium carbonate, NaOH refers to sodium hydroxide, KOH refers to potassium hydroxide, LiOH refers to lithium hydroxide, HCl refers to hydrochloric acid, H_2SO_4 refers to sulfuric acid, $MgSO_4$ refers to magnesium sulfate, and Na_2SO_4 refers to sodium sulfate. 1H NMR refers to proton nuclear magnetic resonance, 13C NMR refers to carbon 13 nuclear magnetic resonance, NOE refers to nuclear overhauser effect, NOESY refers to nuclear overhauser and exchange spectroscopy, COSY refers to homonuclear correlation spectroscopy, HMQC refers to proton detected heteronuclear multiplet-quantum coherence, HMBC refers to heteronuclear multiple-bond connectivity, s refers to singlet, br s refers to broad singlet, d refers to doublet, br d refers to broad doublet, t refers to triplet, q refers to quartet, dd refers to double doublet, m refers to multiplet, ppm refers to parts per million, IR refers to infrared spectrometry, MS refers to mass spectrometry, HRMS refers to high resolution mass spectrometry, EI refers to electron impact, FAB refers to fast atom bombardment, CI refers to chemical ionization, HPLC refers to high pressure liquid chromatography, TLC refer to thin layer chromatography, R_f refers to , R_t refers to retention time, GC refers to gas chromatography, min is minutes, h is hours, rt or RT is room temperature, g is grams, mg is milligrams, L is liters, mL is milliliters, mol is moles and mmol is millimoles.

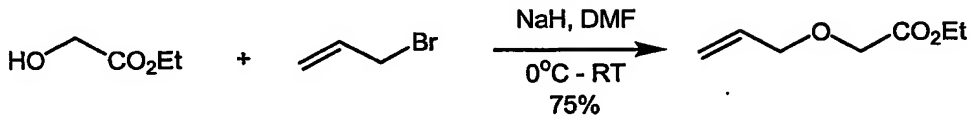
For all of the following examples, standard work-up and purification methods can be utilized and will be obvious to those skilled in the art. Synthetic methodologies that make up the invention are shown in Schemes 1-10. These Schemes are intended to describe the applicable chemistry through the use of specific examples and are not indicative of the scope of the invention.

EXAMPLES

The following non-limiting examples illustrate the inventors' preferred methods for carrying out the process of the invention.

Example 1

Preparation of allyloxy-acetic acid ethyl ester



A round-bottom flask was charged with NaH (1.76 g, 44 mmol, 60% dispersion in mineral oil) and flushed with argon. Hexane (10 ml x 2) was added and decanted. DMF (10 ml) was added into the flask and the resulting solution was cooled to 0°C. Ethyl glycolate (4.16 g, 40.0 mmol) was added over 10 min. The solution was allowed to gradually warm to 25°C and was maintained at that temperature for 2H. The solution was cooled to 0°C and allyl bromide (5.32 g, 44.0 mmol) was added over 10 min. The solution was allowed to gradually warm to 25°C and stirred at that temperature for 2h. Aqueous solution NH_4Cl (10 ml) was added to the reaction and the mixture was diluted with EtOAc (60 ml). The organic layer was separated and washed with H_2O (20 ml x 2), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by distillation under reduced pressure

Yield = 4.29 g, 75%; colorless liquid; bp = 38-39°C, 2 mmHg;

IR (neat): 1985, 1756, 1724, 1203, 1130 cm^{-1};

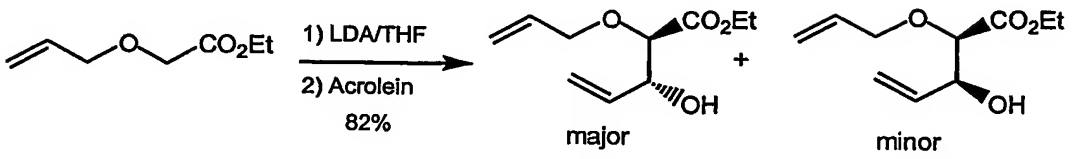
^1H NMR ($CDCl_3$, 400 MHz) δ 5.90-5.70 (m, 1H), 5.25-5.00 (m, 2H), 4.10-4.20 (m, 2H), 3.92-4.05 (m, 4H), 1.21 (t, J = 7Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.09 (C), 133.62 (CH), 117.78 (CH_2), 72.10 (CH_2), 66.99 (CH_2), 60.53 (CH_2), 13.94 (CH_3);

MS (m/z, relative intensity): 144 (M^+, 14), 115 (22), 103 (100), 83 (85); HRMS: calculated for $C_7H_{12}O_3$ (M^+): 144.0786; found 144.0783.

Example 2

Preparation of 2-allyloxy-3-hydroxypent-4-enoic acid ethyl ester



Under an atmosphere of argon, n-BuLi (3 mmol, 1.2 ml, 2.5 M in hexane) was added dropwise to a solution of diisopropylamine (281 mg, 2.78 mmol) in dry THF (20 ml) at –78°C. After stirring for 20-30 min, a solution of allyloxy-acetic acid ethyl ester (200 mg, 1.38 mmol) in THF (4 ml) was added and the mixture was stirred at –78°C for 10 min. Acrolein (79 mg, 1.38 mmol) was added into the reaction mixture and stirring was maintained until all starting materials were consumed. The reaction was quenched by addition of EtOH (2 ml) and warmed to room temperature. The solution was diluted with EtOAc (60 ml), washed with H_2O (20 ml x 2), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography with 20% EtOAc-hexane.

Yield = 961 mg, 82%; colorless liquid; R_f = 0.25 in 20% EtOAc-hexane)

IR (neat): 3300-3600, 2977, 1742, 1364, 1231, 1134, 1028, 927 cm^{-1};

^1H NMR ($CDCl_3$, 400 MHz) δ 6.0-5.8 (m, 2H), 5.3-5.1 (m, 4H), 4.4-4.2 (m, 1H), 4.2-4.0 (m, 3H), 3.9-3.8 (m, 2H), 2.73 (br s, 1H), 1.2 (t, J = 7Hz, 3H);

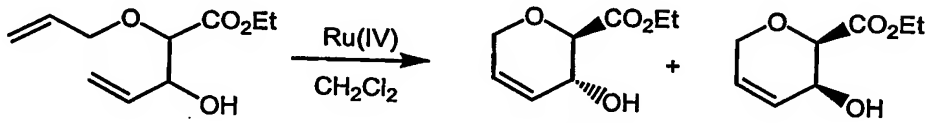
^{13}C NMR ($CDCl_3$, 100 MHz, 2:1 isomeric forms, * denotes minor isomer) δ 170.35* (C), 170.08 (C), 135.77* (CH), 135.42 (CH), 133.56 (CH), 133.47* (CH), 118.23* (CH_2), 118.12 (CH_2), 117.14* (CH_2), 116.96 (CH_2), 80.85 (one CH and one CH*), 73.32* (CH), 72.99 (CH), 71.88* (CH_2), 71.87 (CH_2), 60.99* (CH_2), 60.91 (CH_2), 14.08 (CH_3), 14.05* (CH_3);

MS (m/z, relative intensity): 200 (M^+, 7), 182 (27), 153 (41), 136 (51), 115 (37), 95 (100);

HRMS calculated for $C_{10}H_{16}O_4$ (M^+): 200.1048; found 200.1044.

Example 3

Preparation of 3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester



trans (49%) **cis** (42%)

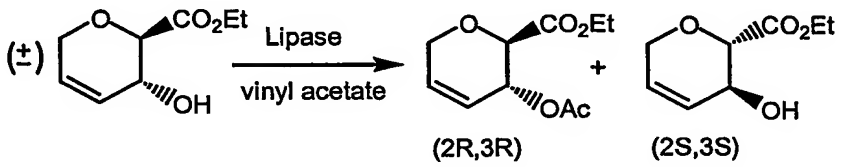
To a solution of 2-allyloxy-3-hydroxypent-4-enoic acid ethyl ester (200 mg, 1.0 mmol) in CH_2Cl_2 (10 ml) was added bis-(tricyclohexylphosphine)-benzylidine ruthenium (IV) chloride (20 mg, 0.024 mmol) and the resulting mixture was stirred at ambient temperature for 4H. Bis-(tricyclohexylphosphine)-benzylidine ruthenium (IV) chloride (20 mg, 0.024 mmol) was added again and the resulting mixture was stirred at ambient temperature for an additional 10 h. The solution was concentrated *in vacuo*. The crude product was purified by flash chromatography with 25 to 30% EtOAc-hexane

trans 3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
Yield = 84 mg (49%); R_f = 0.29 in 40% EtOAc-hexane
IR (neat): 3200-3600, 2976, 1747, 1185, 1111, 1024 cm^{-1}; ^1H NMR (CDC_3, 400 MHz) δ 5.78 (br s, 2H), 4.10-4.35 (m, 5H), 3.93 (d, J = 7Hz, 1H), 3.07 (br s, 1H), 1.24 (t, J = 7Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.58 (C), 127.49 (CH), 126.54 (CH), 77.00 (CH), 64.98 (CH_2), 64.32 (CH), 61.53 (CH_2), 14.00 (CH_3); MS (m/z, relative intensity): 172 (M^+, 2), 141 (6), 112 (16), 81 (100); HRMS calculated for $C_8H_{12}O_4$ (M^+): 172.0735; found 172.0730.

cis 3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
Yield = 69 mg (42%); R_f = 0.06 in 40% EtOAc-hexane
IR (neat): 3200-3600, 2975, 2926, 2841, 1746, 1642, 1182, 1097 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.00-6.15 (m, 1H), 5.90-5.96 (m, 1H), 4.10-4.40 (m, 7H), 1.28 (t, J = 7Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.07 (C), 130.15 (CH), 125.96 (CH), 77.50 (CH), 66.09 (CH_2), 63.48 (CH), 61.36 (CH_2), 14.21 (CH_3); MS (m/z, relative intensity): 172 (M^+, 2), 141 (6), 112 (16), 81 (100); exact mass calculated for $C_8H_{12}O_4$ (M^+): 172.0735; found 172.0730.

Example 4

Resolution of racemic trans-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester using lipase from *Mucor miehei*



(2R,3R) (2S,3S)

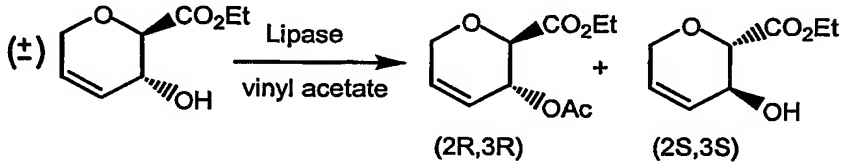
Vinyl acetate (200 μl) was added to a suspension of racemic trans-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (41 mg) and lipase from *Mucor miehei* (50 mg) in 5 ml of toluene. The mixture was agitated for 18H at ambient temperature. The mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography with 20% EtOAc-hexane.

trans-(2R,3R)-3-Acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
Yield = 22 mg (43%); optical purity: >99.9%ee; Colorless liquid; R_f = 0.64 in 40% EtOAc-hexane;
^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.96 (dd, J = 10.4, 1.0 Hz, 1H), 5.80-5.85 (m, 1H), 5.44 (br s, 1H), 4.40 (dd, J = 2.4, 17.3Hz, 1H), 4.10-4.25 (m, 4H), 2.03 (s, 3H), 1.23 (t, J = 7.1Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.25 (C), 168.87 (C), 130.63 (CH), 122.00 (CH), 74.49 (CH), 65.33 (CH), 63.63 (CH_2), 61.50 (CH_2), 20.96 (CH_3), 14.02 (CH_3);

cis-(2S,3S)-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
Yield = 17 mg (42%); optical purity: 89%ee; Colorless liquid, R_f = 0.39 in 40% EtOAc-hexane. IR (neat): 3200-3600, 2976, 1747, 1185, 1111, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.78 (br s, 2H), 4.10-4.35 (m, 5H), 3.93 (d, J = 7Hz, 1H), 3.07 (br s, 1H), 1.24 (t, J = 7Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.58 (C), 127.49 (CH), 126.54 (CH), 77.00 (CH), 64.98 (CH_2), 64.32 (CH), 61.53 (CH_2), 14.00 (CH_3);
HRMS calculated for $C_8H_{12}O_4$ (M^+): 172.0735; found 172.0733.

Example 5

Resolution of racemic trans-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester using lipase from *Alcaligenes sp.*



(2R,3R) (2S,3S)

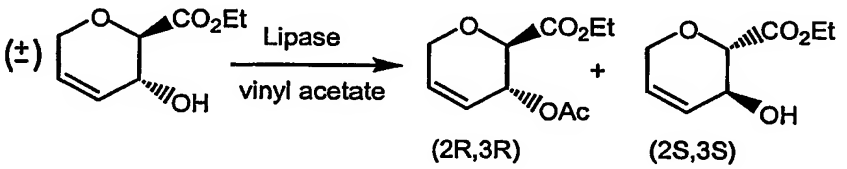
Vinyl acetate (200 µl) was added to a suspension of racemic trans-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (53 mg) and immobilized lipase from *Alcaligenes sp.* (50 mg) in 5 ml of toluene. The mixture was agitated for 14H at ambient temperature. The mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography with 20% EtOAc-hexane.

trans-(2R,3R)-3-Acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
Yield = 32 mg (49%); optical purity: >95%ee;

trans-(2S,3S)-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
Yield = 25 mg (47%); optical purity: >99.9%ee;

Example 6

Resolution of racemic trans-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester using lipase from *Candida antartica, type A*



(2R,3R) (2S,3S)

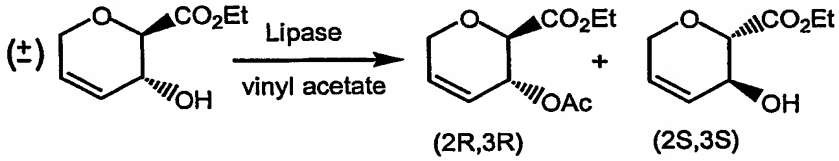
Vinyl acetate (10 µl) was added to a suspension of racemic trans-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (5 mg) and lipase from *Candida antartica, type A* (11 mg) in 1 ml of toluene. The mixture was agitated for 24H at ambient temperature. The mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography with 20% EtOAc-hexane.

trans-(2R,3R)-3-Acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
optical purity: >99.5%ee;

trans-(2S,3S)-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
optical purity: 88%ee;

Example 7

Resolution of racemic trans-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester using lipase from *Alcaligenes sp.*



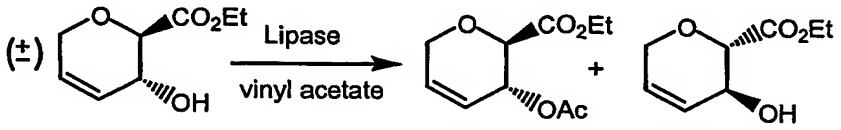
Vinyl acetate (10 μl) was added to a suspension of racemic trans-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (5 mg) and lipase from *Alcaligenes sp.* (11 mg) in 1 ml of toluene. The mixture was agitated for 24H at ambient temperature. The mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography with 20% EtOAc-hexane.

trans-(2R,3R)-3-Acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
optical purity: >99.5%ee;

trans-(2S,3S)-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
optical purity: 98.8%ee;

Example 8

Resolution of racemic trans-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester using lipase from *Pseudomonas cepacia*



(2R,3R) (2S,3S)

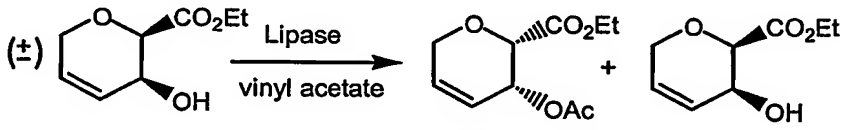
Vinyl acetate (10 µl) was added to a suspension of racemic trans-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (6 mg) and lipase from *Pseudomonas cepacia* (12 mg) in 1 ml of toluene. The mixture was agitated for 4H at ambient temperature. The mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography with 20% EtOAc-hexane.

trans-(2R,3R)-3-Acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
optical purity: >99.5%ee;

trans-(2S,3S)-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
optical purity: 99.4%ee;

Example 9

Resolution of racemic cis-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester using lipase from *Mucor miehei*



(2S,3R) (2R,3S)

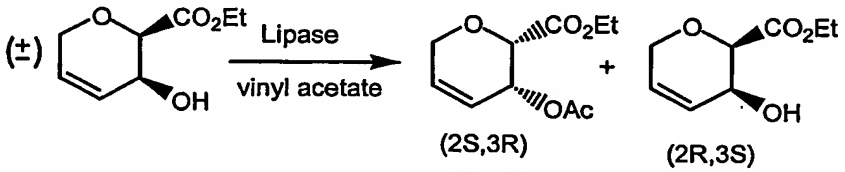
Vinyl acetate (200 µl) was added to a suspension of racemic cis-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (42 mg) and lipase from *Mucor miehei* (53 mg) in 5 ml of toluene. The mixture was agitated for 18H at ambient temperature. The mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography with 20% EtOAc-hexane.

cis-(2S,3R)-3-Acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
Yield = 24 mg (44%); optical purity: >99.9%ee; Colorless liquid; R_f = 0.34 in 70% EtOAc-hexane;
IR (neat): 2980, 2932, 2831, 1738, 1375, 1234, 1105, 1023 cm^{-1};
^1H NMR ($CDCl_3$, 400 MHz) δ 5.95-6.10 (m, 2H), 5.30-5.35 (m, 1H), 4.41 (dd, J = 3.4, 1.6Hz, 1H), 4.15-4.40 (m, 4H), 2.00 (s, 3H), 1.25 (t, J = 7.2Hz, 3H);
^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.12 (C), 167.91 (C), 132.06 (CH), 121.72 (CH), 75.12 (CH), 65.77 (CH_2), 64.87 (CH), 61.33 (CH_2), 20.67 (CH_3), 14.14 (CH_3);
MS (m/z, relative intensity): 215 (M^++1, 6), 213 (M^+-1, 18), 153 (100), 149 (30);
HRMS calculated for $C_{10}H_{14}O_5$ (M^+): 214.0841; found 214.0839.

cis-(2R,3S)-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
Yield = 20 mg (48%); optical purity: 89%ee; Colorless liquid; R_f = 0.61 in 70% EtOAc-hexane;
IR (neat): 3200-3600, 2975, 2926, 2841, 1746, 1642, 1182, 1097 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.00-6.15 (m, 1H), 5.90-5.96 (m, 1H), 4.10-4.40 (m, 7H), 1.28 (t, J = 7Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.07 (C), 130.15 (CH), 125.96 (CH), 77.50 (CH), 66.09 (CH_2), 63.48 (CH), 61.36 (CH_2), 14.21 (CH_3);
MS (m/z, relative intensity): 172 (M^+, 2), 141 (6), 112 (16), 81 (100); exact mass calculated for $C_8H_{12}O_4$ (M^+): 172.0735; found 172.0730.

Example 10

Resolution of racemic cis-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester using lipase from *Alcaligenes sp.*



Vinyl acetate (200 μl) was added to a suspension of racemic cis-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (57 mg) and lipase from *Alcaligenes sp.* (51 mg) in 5 ml of toluene. The mixture was agitated for 14H at ambient temperature. The

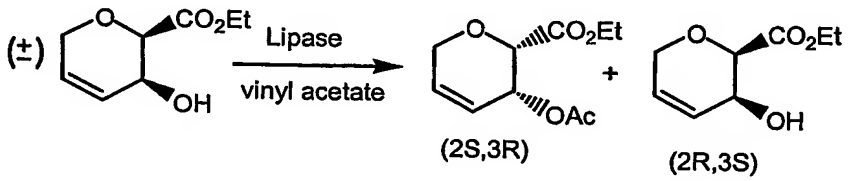
mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography with 20% EtOAc-hexane.

cis-(2S,3R)-3-Acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
Yield = 32 mg (49%); optical purity: 98.8%ee;

cis-(2R,3S)-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
Yield = 27 mg (48%); optical purity: >99.9%ee;

Example 11

Resolution of racemic cis-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester using lipase from *Candida Rugosa*



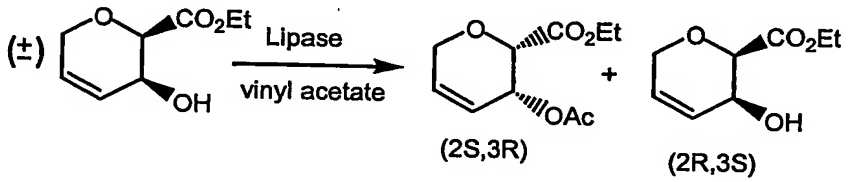
Vinyl acetate (10 μl) was added to a suspension of racemic cis-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (4 mg) and lipase from *Candida Rugosa* (20 mg) in 1 ml of toluene. The mixture was agitated for 34H at ambient temperature. The mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography with 20% EtOAc-hexane.

cis-(2S,3R)-3-Acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
optical purity: >99.5%ee;

cis-(2R,3S)-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
optical purity: >99.5%ee;

Example 12

Resolution of racemic cis-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester using lipase from *Candida antartica, type A*



(2S,3R) (2R,3S)

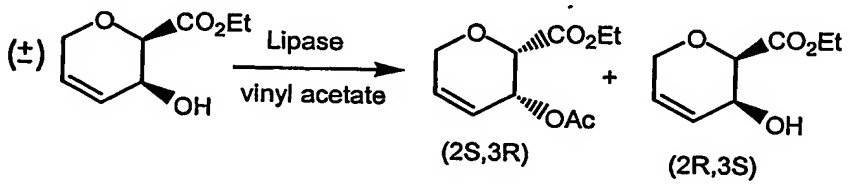
Vinyl acetate (10 µl) was added to a suspension of racemic cis-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (4 mg) and lipase from *Candida antartica, type A* (11 mg) in 1 ml of toluene. The mixture was agitated for 20 h at ambient temperature. The mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography with 20% EtOAc-hexane.

cis-(2S,3R)-3-Acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
optical purity: >99.5%ee;

cis-(2R,3S)-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
optical purity: >99.5%ee;

Example 13

Resolution of racemic cis-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester using lipase from *Pseudomonas cepacia*



(2S,3R) (2R,3S)

Vinyl acetate (10 µl) was added to a suspension of racemic cis-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (4 mg) and lipase from *Pseudomonas cepacia* (9 mg) in 1 ml of toluene. The mixture was agitated for 4H at ambient temperature. The

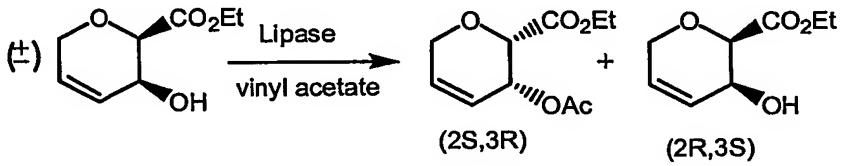
mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography with 20% EtOAc-hexane.

cis-(2S,3R)-3-Acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester optical purity: >99.5%ee;

cis-(2R,3S)-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester optical purity: >99.5%ee;

Example 14

Resolution of racemic cis-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester using lipase from *Pseudomonas fluorescens*



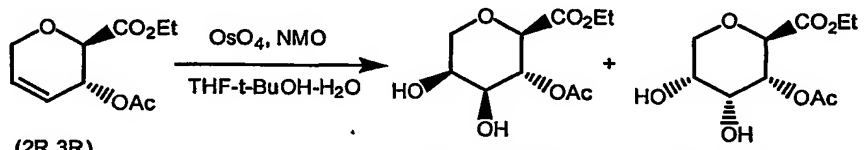
Vinyl acetate (10 μl) was added to a suspension of racemic cis-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (4 mg) and lipase from *Pseudomonas fluorescens* (10 mg) in 1 ml of toluene. The mixture was agitated for 38H at ambient temperature. The mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography with 20% EtOAc-hexane.

cis-(2S,3R)-3-Acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester optical purity: >99.5%ee;

cis-(2R,3S)-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester optical purity: >99.5%ee;

Example 15

Preparation of (2R,3R,4S,5S)- and (2R,3R,4R,5R)-3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid ethyl esters



(2R,3R) (2R,3R,4S,5S) 50% (2R,3R,4R,5R) 10%

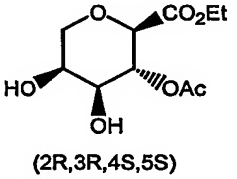
To (2R,3R)-3-acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (300 mg, 1.40 mmol) in 27 ml of THF-tert-BuOH-H_2O (6:17.7:3 ml) was added NMO (612 mg, 4.47 mmol) and the solution was stirred for 5 min at ambient temperature. OsO_4 (0.3 ml, 2.5 wt% in tert-BuOH) was added and the mixture was stirred at ambient temperature for 72H. Sodium hydrosulphite (1.2 g), Florisil (12.0 g) and H_2O (10 ml) were added sequentially and the mixture was stirred for 30 min, washed with acetone (500ml), filtered through filter paper and extracted with EtOAc (2 x 300 ml) *in vacuo*. The crude product was purified by flash chromatography with 90% EtOAc-hexane to give (2R,3R,4S,5S)- and (2R,3R,4R,5R)-3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid ethyl esters in 60% yield.

(2R,3R,4R,5R)-3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester
Colorless oil; Yield: 10%; R_f= 0.53 in EtOAc
IR (neat): 3600-3200, 2952, 2925, 2868, 1738, 1458, 1375, 1242, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.83-4.90 (m, 1H), 4.22-4.32 (m, 3H), 4.15 (d, J=9.0 Hz, 1H), 3.80-3.90 (m, 2H), 3.74 (dd, J=10.1, 10.8Hz, 1H), 2.09 (s, 3H), 1.31 (t, J=7.2Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.29 (C), 170.28 (C), 74.48 (CH), 69.44 (CH), 68.85 (CH), 67.39 (CH), 63.23 (CH_2), 62.32 (CH_2), 21.29 (CH_3), 14.48 (CH_3); EIMS (m/z, relative intensity): 248 (M^+, 2), 206 (4), 145 (30), 97 (20), 57 (38), 43 (100).

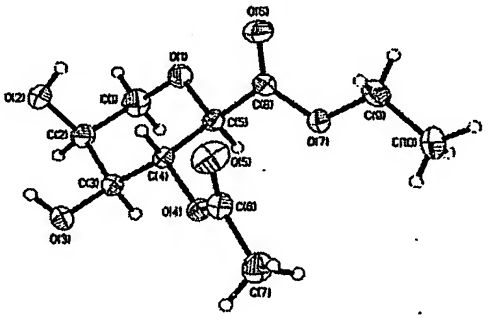
(2R,3R,4S,5S)-3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester
Colorless liquid, Yield: 50%; R_f= 0.5 in EtOAc
IR (neat): 3640-3080, 2983, 1739, 1375, 1242, 1107, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.20 (dd, J = 8.4, 8.4Hz, 1H), 4.08-4.20 (m, 3H), 3.98 (d, J=1.7Hz, 1H), 3.84 (d,

J=8.3Hz, 1H), 3.75 (d, J=8.4Hz, 1H), 3.58 (dd, J=10.6, 1.7Hz, 1H), 3.09 (s, 3H), 2.07 (s, 3H), 1.24 (t, J = 7.2Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 170.83 (C), 168.48 (C), 75.95 (CH), 71.33 (CH), 70.82 (CH), 68.59 (CH_2), 67.84 (CH), 61.85 (CH_2), 20.85 (CH_2), 13.94 (CH_3); EIMS (m/z, relative intensity): 248 (M^+, 1), 230 (3), 205 (18), 157 (26), 115 (40), 97 (68), 43 (100); exact mass calculated for $C_{10}H_{16}O_7$ (M^+): 248.0896; found 248.0887

X-ray crystal structure of (2R,3R,4S,5S)-3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester

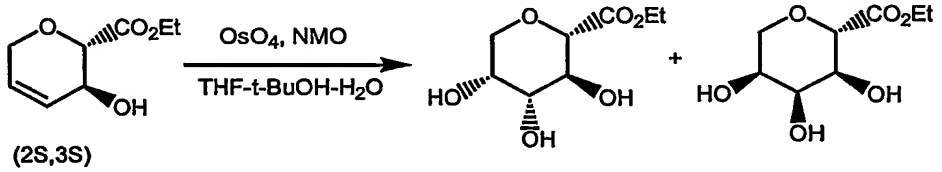


(2R,3R,4S,5S)



Example 16

Preparation of (2S,3S,4R,5R)- and (2S,3S,4S,5S)-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid ethyl esters



(2S,3S) (2S,3S,4R,5R) 50% (2S,3S,4S,5S) 10%

To (2S,3S)-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (100 mg, 0.58 mmol) in 9 ml of THF-tert-BuOH-H_2O (2:5.9:1) was added NMO (235 mg, 1.72 mmol) and the solution was stirred for 5 min at ambient temperature. OsO_4 (0.1 ml, 2.5wt% in tert-BuOH) was added and the mixture was stirred at ambient temperature for 24H. Sodium hydrosulphite (0.4 g), Florisil (4.0 g) and H_2O (10 ml) were sequentially added and the mixture was stirred for 30 minutes, washed with acetone (200 ml), filtered through filter paper and extracted with EtOAc (2 x 100 ml). The combined organic layers were washed with brine (100 ml), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography with 90% EtOAc-hexane to give

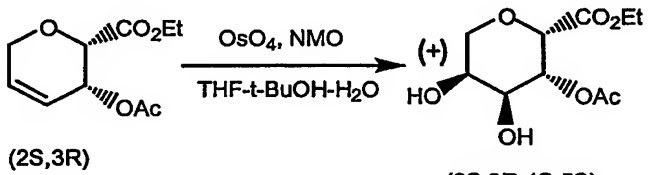
(2S,3S,4R,5R)- and (2S,3S,4S,5S)-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid ethyl esters in 60% yield.

(2S,3S,4R,5R)-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester
Colorless oil; Yield: 50%;
IR (neat): 3640-3080, 2980, 2920, 1732, 1235, 1102, 629 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.34 (br s, 3H), 4.21 (q, J = 7.2Hz, 2H), 4.05 (d, J=1.7Hz, 1H), 4.04 (dd, J=12.6, 1.7Hz, 1H), 3.90-3.98 (m, 1H), 3.68 (d, J=9.4Hz, 1H), 3.66-3.60 (m, 1H), 3.55 (d, J=12.2Hz, 1H), 1.27 (t, J = 7.2Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 170.30 (C), 78.88 (CH), 73.84 (CH), 70.27 (CH_2), 68.92 (CH), 68.70 (CH), 61.84 (CH_2), 13.99 (CH_3); EIMS (m/z, relative intensity): 207 (M^++1, 100), 133 (5), 115 (7), 73 (32), 57 (12); exact mass calculated for $C_8H_{14}O_6$ (M^+): 206.0790; found 206.0788.

(2S,3S,4S,5S)-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester
Colorless oil; Yield: 10%;
IR (neat): 3640-3080, 2980, 2926, 1732, 1645, 1381, 1204, 1099, 1043 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.22-4.30 (m, 2H), 4.11-4.13 (d, J = 8.6Hz, 1H), 3.70-3.90 (m, 3H), 3.52-3.62 (m, 2H), 1.30 (t, J = 7.2Hz, 3H); EIMS (m/z, relative intensity): 206 (M^+, 17), 188 (4), 167 (18), 149 (49), 73 (70), 57 (83), 43(100);

Example 17

Preparation of (+)-(2S,3R,4S,5S)-3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester



(2S,3R) (2S,3R,4S,5S)

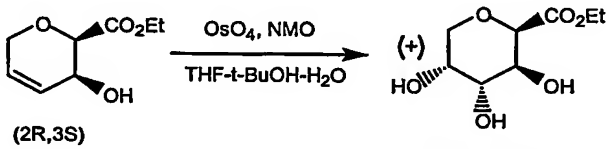
To (2S,3R)-3-acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (200 mg, 0.93 mmol) in 18ml of THF-tert-BuOH-H_2O (4:11.8:2) was added NMO (408 mg, 2.98 mmol) and the solution was stirred for 5 min at ambient temperature. OsO_4 (0.2 ml, 2.5wt% in tert-BuOH) was added and the solution was stirred at ambient temperature for 72H.

Sodium hydrosulphite (0.83 g), Florisil (2.0 g) and H_2O (2 ml) were added sequentially and the mixture was stirred for 30 minutes, washed with 200 ml EtOAc, filtered through filter paper and the solvent was evaporated. The crude product was purified by flash chromatography with 20-80% EtOAc-hexane to give (2S,3R,4S,5S)-3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester

Yield: 65%; Colorless oil; R_f= 0.4 in 100% EtOAc;
IR (neat): 3600-3200, 2923, 2851, 1740, 1483, 1376, 1233, 1121, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.21 (dd, J=1.7Hz, 3.8Hz, 1H), 4.45 (d, J=1.7Hz, 1H), 4.14-4.20 (m, 2H), 4.02-4.04 (m, 1H), 3.81-3.94 (m, 2H), 3.55 (dd, J=10.2, 10.2Hz, 1H), 3.31 (br s, 2H), 2.02 (s, 3H), 1.21 (t, J=7.2Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 170.13 (C), 168.75 (C), 72.42 (CH), 71.93 (CH), 66.97 (CH), 65.52 (CH_2), 64.08 (CH), 61.63 (CH_2), 20.61 (CH_3), 14.00 (CH_3); EIMS (m/z, relative intensity): 249 (M^++1, 5), 206 (8), 175 (10), 157 (39), 115 (37), 43 (100); exact mass calculated for $C_{10}H_{16}O_7$ (M^+): 248.0896; found 248.0887.

Example 18

Preparation of (+)-(2R,3S,4R,5R)-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester



(2R,3S) (2R,3S,4R,5R)

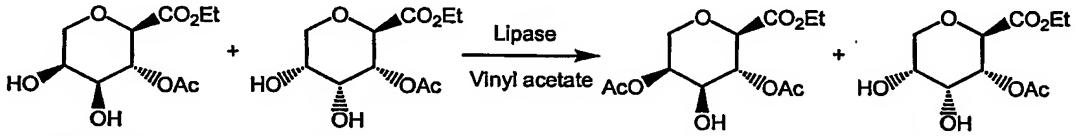
To (2R,3S)-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (200 mg, 1.16 mmol) in 18 ml THF-tert-BuOH-H_2O (4:11.8:2) was added NMO (408 mg, 3.43 mmol) and the solution was stirred for 5 min at ambient temperature. OsO_4 (0.2 ml, 2.5wt% in tert-BuOH) was added and the mixture was stirred at ambient temperature for 72H. Sodium hydrosulphite (0.83 g), Florisil (2.0 g) and H_2O (2 ml) were added sequentially and the mixture was stirred for 30 minutes, washed with 200 ml EtOAc, filtered through filter paper and the solvent was evaporated. The crude product was purified by flash chromatography with 20-80% EtOAc-hexane to give (2R,3S,4R,5R)-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester

Yield = 65%; Colorless oil; R_f = 0.4 in 100% EtOAc;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.36 (s, 1H), 4.18-4.26 (m, 2H), 4.00-4.16 (m, 6H), 3.80-3.90 (m, 1H), 3.48-3.58 (m, 1H), 1.26 (t, J=7.1Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.59 (C), 74.20 (CH), 70.75 (CH), 69.69 (CH), 65.56 (CH_2), 64.10 (CH), 61.74 (CH_2), 14.04 (CH_3); EIMS (m/z, relative intensity): 207 (M^++1, 11), 206 (19), 133 (23), 115 (61), 73 (85), 57 (80), 43 (100); Exact mass calculated for $C_8H_{14}O_6$ (M^+): 206.0790; found 206.0787.

Example 19

Preparation of (2R,3R,4S,5S)-3,5-diacetoxy-4-hydroxy-tetrahydropyran-2-carboxylic acid ethyl ester using lipase from *Alcaligenes sp.*



(2R,3R,4S,5S) 25 mg + (2R,3R,4R,5R) 25 mg → (2R,3R,4S,5S) 20 mg + (2R,3R,4R,5R) 10 mg

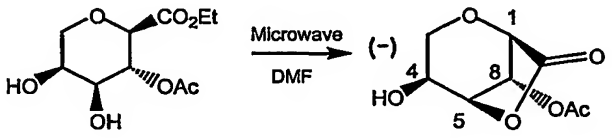
To a 1:1 mixture of (2R,3R,4S,5S)- and (2R,3R,4R,5R)-3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid ethyl esters (50 mg, 0.2 mmol) in toluene (3 ml) was added *Alcaligenes sp.* (40 mg) followed by vinyl acetate (26 µl). The solution was stirred for 5H at ambient temperature, filtered and the solvent was removed *in vacuo*. The product was purified by flash chromatography with 20% EtOAc-hexane to give 20 mg of (2R,3R,4S,5S)-3,5-diacetoxy-4-hydroxy-tetrahydropyran-2-carboxylic acid ethyl ester 10 mg of the (2R,3R,4R,5R) diol.

(2R,3R,4S,5S)-3,5-diacetoxy-4-hydroxy-tetrahydropyran-2-carboxylic acid ethyl ester
Colorless oil; R_f = 0.75 in 100% EtOAc.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.27 (d, J = 8.2Hz, 1H), 5.10-5.13 (m, 1H), 4.12-4.25 (m, 4H), 3.90-3.95 (m, 2H), 2.14 (s, 3H), 2.10 (s, 3H), 1.27 (t, J = 7.2Hz, 3H).

Example 20

Preparation of (-)-(1R,4S,5S,8R)-8-acetoxy-4-hydroxy-2,6-dioxa-bicyclo[3.2.1]octan-7-one



(2R,3R,4S,5S) (1R,4S,5S,8R)

(2R,3R,4S,5S)-3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester (300 mg, 1.2 mmol) was dissolved in DMF (5 ml) and the solution was subjected to microwave irradiation at 150°C for 4H. After cooling, the solvent was removed *in vacuo*. The crude product was purified by flash chromatography with 20% EtOAc-hexane to give (-)-(1R,4S,5S,8R)-8-acetoxy-4-hydroxy-2,6-dioxa-bicyclo[3.2.1]octan-7-one.

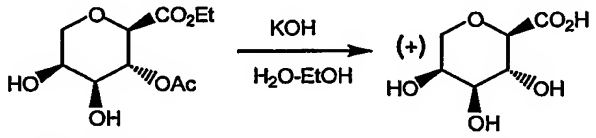
Yield = 12%;

IR (neat): 2957, 2923, 2852, 1733, 1463, 1260, 1092, 1019, 799 cm^{-1};

^1H NMR ($CDCl_3$, 400 MHz) δ 4.77 (br s, 1H), 4.58 (br s, 1H), 4.41 (br s, 1H), 4.03 (dd, J = 10.5, 2.8Hz, 1H), 3.96 (d, J = 10.5Hz, 1H), 3.86 (br s, 1H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 171.82 (C), 167.19 (C), 79.35 (CH), 77.32 (CH), 72.02 (CH), 70.71 (CH), 64.90 (CH_2), 20.70 (CH_3); EIMS (m/z, relative intensity): 279 (M^++77, 17), 160 (37), 159 (57), 148(62), 54(70), 42(99), 31(100);

Example 21

Preparation of (+)-(2R,3R,4S,5S)-3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid



(2R,3R,4S,5S) (2R,3R,4S,5S)

A solution of (2R,3R,4S,5S)-3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid ethyl ester (370 mg, 1.49 mmol) in 19 ml of water-ethanol (4:1) was cooled to 0°C and

1M KOH (2.1 ml) was added dropwise over 30 min. The resulting solution was stirred at 0°C for 30 min and neutralized by addition of DOWEX-50W-X8 ion exchange resin. The resin was removed by filtration and the filtrate was concentrated *in vacuo*. The crude product was triturated with isopropanol (2 ml) to afford acid (+)-(2R,3R,4S,5S)-3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid.

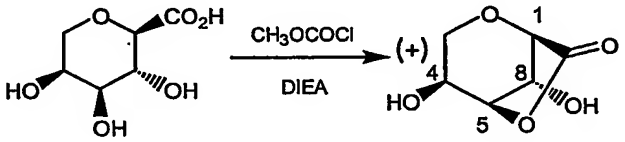
Yield = 65%;

IR (neat): 3600-3100, 2924, 1731, 1243, 1101, 1064, 778, 628 cm^{-1};

^1H NMR (CD_3OD, 400 MHz) δ 3.84-3.88 (m, 1H), 3.75-3.86 (m, 4H), 3.61 (d, J = 8.4Hz, 1H), 3.49-3.51 (m, 1H), 3.45-3.48 (m, 2H); ^{13}C NMR (CD_3OD, 100MHz) δ 173.12 (C), 80.10 (CH), 74.54 (CH), 70.40 (CH), 70.39 (CH_2), 69.52 (CH); EIMS (m/z, relative intensity): 177 (M^+-1, 5), 160 (12), 149 (22), 73 (43), 57 (65), 43 (100).

Example 22

Preparation of (+)-(1R,4S,5S,8R)-4,8-hydroxy-2,6-dioxa-bicyclo[3.2.1]octan-7-one



(2R,3R,4S,5S) (1R,4S,5S,8R)

To (2R,3R,4S,5S)-3-acetoxy-4,5-dihydroxy-tetrahydropyran-2-carboxylic acid (25 mg, 0.14 mmol) was added diisopropylethylamine (30 μL, 0.169 mmol) followed by dry THF (3 ml) and the resulting solution was cooled to 0°C. Methyl chloroformate (12 μL, 0.154 mmol) was added dropwise over 5 min and the reaction mixture was stirred at room temperature for 36H. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography with 70% EtOAc-hexane to give (+)-(1R,4S,5S,8R)-4,8-hydroxy-2,6-dioxa-bicyclo[3.2.1]octan-7-one

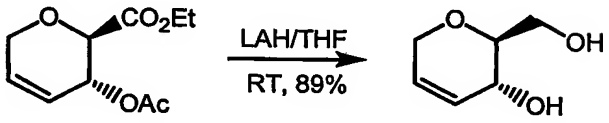
Yield = 50%;

IR (neat): 3550-3100, 2924, 1732 cm^{-1};

^1H NMR (CD_3OD, 200 MHz) δ 3.80-4.05 (m, 2H), 3.62-3.78 (m, 2H), 3.50-3.60 (m, 1H), 3.20-3.30 (m, 1H).

Example 23

Preparation of trans-2-hydroxymethyl-3,6-dihydro-2H-pyran-3-ol



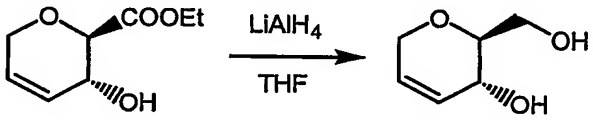
To a solution of trans-3-acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (56 mg, 0.26 mmol) in THF (5 ml) was added $LiAlH_4$ (62 mg, 1.64 mmol). The resulting solution was stirred at ambient temperature for 15 min and quenched by addition of H_2O (10 ml). The solution was diluted with EtOAc (50 ml x 2), washed with brine (50 ml), dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography with 20% EtOAc-hexane (R_f = 0.25 in EtOAc) to give 2-hydroxymethyl-3,6-dihydro-2H-pyran-3-ol as a colorless liquid

Yield: 30 mg, 89%.

IR (neat): 3100-3600, 2983, 1642, 1376, 1186, 1114, 1038 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.77-5.84 (m, 2H), 4.16-4.19 (m, 3H), 3.88 (dd, J = 11.5, 3.9Hz, 1H), 3.78 (dd, J = 11.5, 5.5Hz, 1H), 3.30-3.33 (m, 1H), 1.77 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 128.41 (CH), 127.80 (CH), 78.46 (CH), 65.31 (CH_2), 64.42 (CH), 63.24 (CH_2); MS (m/z, relative intensity): 130 (M^+, 8), 112 (29), 97 (61), 81 (100); exact mass calculated for $C_6H_{10}O_3$ (M^+): 130.0630; found 130.0633.

Example 24

Preparation of trans-2-hydroxymethyl-3,6-dihydro-2H-pyran-3-ol



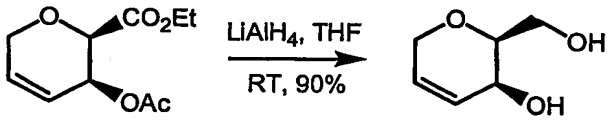
To a stirred solution of trans-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (0.480 g, 2.79 mmol) in THF (20 ml) at RT, was added in portions $LiAlH_4$ (0.126 g, 3.384 mmol) and the resulting mixture was stirred for 30 min. EtOAc (10 ml) was added, the mixture was stirred for 10 min and extracted with water (10 ml x 2). The organic layer

was dried over anhydrous Na_2SO_4. The solvent was removed in *vacuo* and the crude product purified by flash chromatography (25-30% EtOAc in hexane).

Yield: 0.37 g, 94%;

Example 25

Preparation of cis-2-hydroxymethyl-3,6-dihydro-2H-pyran-3-ol

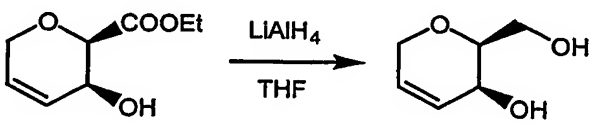


To a solution of cis-3-acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (52 mg, 0.25 mmol) in THF (5 ml) was added $LiAlH_4$ (60 mg, 1.60 mmol). The resulting solution was stirred at ambient temperature for 15 min. The reaction was quenched by addition of H_2O (10 ml). The solution was diluted with EtOAc (50 ml x 2), washed with brine (50 ml), dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography with 20% EtOAc-hexane to give cis-2-hydroxymethyl-3,6-dihydro-2H-pyran-3-ol

Colorless liquid; Yield: 28 mg, 90%; R_f = 0.20 in EtOAc
IR (neat): 3050-3600, 2932, 1644, 1447, 1378, 1297, 1185, 1103, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.95-6.05 (m, 2H), 4.12-4.30 (m, 2H), 3.88-3.94 (m, 2H), 3.75-3.85 (m, 1H), 3.55-3.60 (m, 1H), 1.86 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 130.60 (CH), 126.41 (CH), 77.87 (CH), 66.18 (CH_2), 63.50 (CH), 63.11 (CH_2); MS (m/z, relative intensity): 129 (M^+-1, 22), 112 (5), 111 (17), 70 (100); exact mass calculated for $C_6H_{10}O_3$ (M^+): 130.0630; found 130.0634.

Example 26

Preparation of cis-2-hydroxymethyl-3,6-dihydro-2H-pyran-3-ol

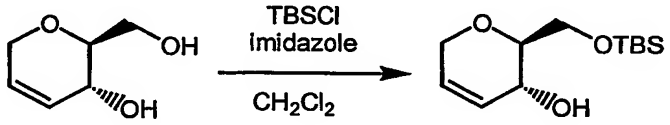


To a stirred solution of cis-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (0.60 g, 3.48 mmol) in THF (20 ml) at RT, was added in portions $LiAlH_4$ (0.204 g, 4.89 mmol) and the resulting mixture was stirred for 30 min. EtOAc (10 ml) was added, the mixture was stirred for 10 min and extracted with water (10 ml x 2). The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed in *vacuo* and the crude product purified by flash chromatography (25-30% EtOAc in hexane).

Colorless oil; Yield: 0.42 g, 85%. R_f = 0.18 (EtOAc).

Example 27

Preparation of trans-2-(tert-butyldimethylsilanyloxymethyl)-3,6-dihydro-2H-pyran-3-ol

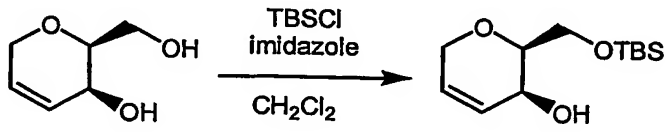


To a 0°C, stirred solution of trans-2-hydroxymethyl-3,6-dihydro-2H-pyran-3-ol (0.4 g, 2.84 mmol) in CH_2Cl_2 (40 ml) under an Argon atmosphere was added imidazole (0.231 g, 3.4 mmol) followed by TBSCl (0.428 g, 3.4 mmol). The resulting mixture was stirred for 1H at 0°C. The reaction mixture was washed with water (10 ml x 2) and brine (10 ml). The organic phase was dried over anhydrous Na_2SO_4. The solvent was removed in *vacuo* and the crude product purified by flash chromatography (25-40% EtOAc in hexane).

Colorless oil. Yield: 0.618 g, 84%. R_f = 0.72 (1:1 ether-hexane).
IR (neat): 3600-3100, 3037, 2929, 2857, 1463, 1254, 1099, 837, 778 cm^{-1};
^1H NMR ($CDCl_3$, 400 MHz) δ 5.76-5.77 (m, 2H), 4.15-4.20 (m, 1H), 4.06-4.10 (m, 2H), 3.89 (dd, J = 10.0, 5.2Hz, 1H), 3.71 (dd, J = 7.4, 10.0 Hz, 1H), 3.30-3.36 m, 1H), 0.88 (s, 9H), 0.08 (s, 6H);
^{13}C NMR ($CDCl_3$, 100 MHz) δ 127.97 (CH), 127.05 (CH), 77.32 (CH), 67.02 (CH), 65.73 (CH_2), 65.21 (CH_2), 25.83 (3 x CH_3), 18.21 (C), -5.53 (CH_3), -5.59 (CH_3),
MS (m/z, relative intensity): 189 (4, M^+-*tert*-But), 118 (78), 116 (100)

Example 28

Preparation of cis-2-(tert-butyldimethylsilanyloxymethyl)-3,6-dihydro-2H-pyran-3-ol



To a 0°C, stirred solution of cis-2-hydroxymethyl-3,6-dihydro-2H-pyran-3-ol (0.4 g, 2.84 mmol) in CH_2Cl_2 (40 ml) under an Argon atmosphere was added imidazole (0.231 g, 3.4 mmol) followed by TBSCl (0.428 g, 3.4 mmol). The resulting mixture was stirred for 1H at 0°C. The reaction mixture was washed with water (10 ml x 2) and brine (10 ml). The organic phase was dried over anhydrous Na_2SO_4. The solvent was removed in *vacuo* and the crude product purified by flash chromatography (25-40% EtOAc in hexane).

Colorless oil. Yield: 0.478 g, 65%. R_f= 0.6 (1:1, ether-hexane).

IR (neat): 3500-3150, 2928, 2925, 1103 cm^{-1};

^1H NMR ($CDCl_3$, 400 MHz) δ 5.99-6.03 (m, 1H), 5.89-5.93 (m, 1H), 4.19 (dd, J = 3.4, 1.7Hz, 1H), 4.11 (dd, J = 16.9, 2.0 Hz, 1H), 3.93-3.95 (m, 1H), 3.50-3.85 (m, 2H), 3.49-3.52 (m, 1H), 1.90-2.00 (m, 1H), 0.88 (s, 9H), 0.07 (s, 6H)

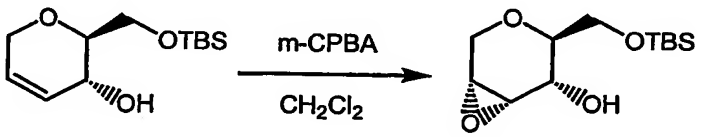
^{13}C NMR ($CDCl_3$, 100 MHz) δ 130.26 (CH), 126.62 (CH), 78.12 (CH), 66.14 (CH_2), 62.85 (CH_2), 62.57 (CH), 25.87 (3 x CH_3), 18.28 (C), -5.36 (CH_3), -5.41 (CH_3)

MS (m/z, relative intensity): 203 (M+-41), 185 (25), 173 (48), 143 (41), 131 (71), 117 (100).

MS (EI) calcd. for $C_{12}H_{24}O_3Si$ 244.1495.

Example 29

Preparation of 4-(tert-buyldimethylsilanyloxymethyl)-3,7-dioxa-bicyclo[4.1.0]heptan-5-ol



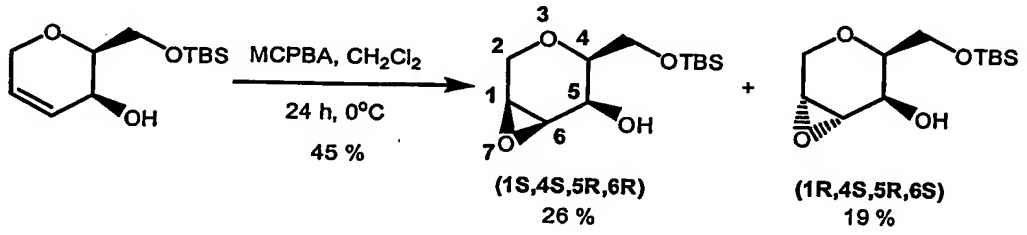
To a 0°C, stirred solution of trans-2-(tert-butyldimethylsilanyloxymethyl)-3,6-dihydro-2H-pyran-3-ol (0.110 g, 0.45 mmol) in CH_2Cl_2 (10 ml) was added m-CPBA (75%, 0.108 g, 1.08 mmol) and the mixture was stirred for 1h at 0°C. Dimethyl sulfide (0.01 ml) was added and stirring was continued for 10 min. The solvent was removed in *vacuo* and the crude product was diluted with EtOAc (30 ml). The resulting solution was washed successively with saturated aqueous Na_2CO_3 (10 ml), water (10 ml x 2) and brine (10 ml). The organic phase was dried over anhydrous Na_2SO_4. The solvent was removed in *vacuo* and the crude product was purified by flash chromatography (25-40% EtOAc in hexane).

Colorless oil. Yield: 0.094 g, 80%. R_f = 0.47 (1:1 ether-hexane).

IR (neat): 3550-3100, 2954, 2928, 2856, 1463, 1254, 1146, 1102, 837, 778 cm^{-1};
^1H NMR (acetone-d_6, 400 MHz) δ 4.11 (d, J = 7.2Hz, 1H), 4.03 (dd, J = 13.4, 3.9Hz, 1H), 3.87 (dd, J = 10.5, 2.2Hz, 1H), 3.84-3.81 (m, 1H), 3.73-3.64 (m, 2H), 3.45 (dd, J = 4.2, 4.2Hz, 1H), 3.35-3.38 (m, 1H), 3.20-3.15 (m, 1H), 0.89 (s, 9H), 0.05 (s, 6H);
^{13}C NMR (acetone-d_6, 100 MHz) δ 76.75 (CH), 66.45 (CH), 65.19 (CH_2), 64.31 (CH_2), 55.73 (CH), 54.95 (CH), 26.25 (3 x CH_3), 18.90 (C), -5.11 (CH_3), -5.14 (CH_3);
MS (m/z, relative intensity): 203 (M^+-*t*-Bu, 17), 173 (3), 117 (53), 75 (100).

Example 30

Preparation of (1S,4S,5R,6R)- and (1R,4S,5R,6S)-4-(tert-butyl-dimethylsilanyloxy-methyl)-3,7-dioxa-bicyclo[4.1.0]heptan-5-ol



(1S,4S,5R,6R)
26 %

(1R,4S,5R,6S)
19 %

To a 0°C, stirred solution of cis-2-(tert-butyldimethylsilanyloxymethyl)-3,6-dihydro-2H-pyran-3-ol (0.200 g, 0.91 mmol) in CH_2Cl_2 (15 ml) was added m-CPBA (75%, 0.46 g, 2.68 mmol) and the mixture was stirred for 1H at 0°C. Dimethyl sulfide (0.01 ml) was

added and stirring was continued for 10 min. The solvent was removed in *vacuo* and the crude product was diluted with EtOAc (30 ml). The resulting solution was washed successively with saturated aqueous Na_2CO_3 (10 ml), water (10 ml x 2) and brine (10 ml). The organic phase was dried over anhydrous Na_2SO_4. The solvent was removed in *vacuo* and the crude product was purified by flash chromatography (25-40% EtOAc in hexane).

(1S,4S,5R,6R)-4-(tert-butyl-dimethylsilanyloxymethyl)-3,7-dioxa-bicyclo[4.1.0]heptan-5-ol

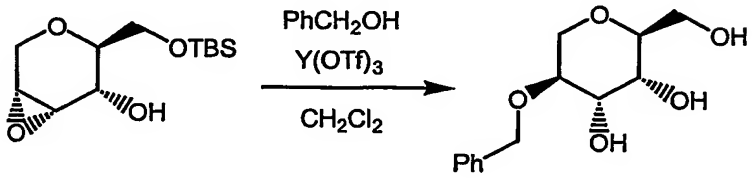
Yield: 0.083 g, 39%. R_f = 0.52 (30% EtOAc-hexane).
IR (neat): 3550-3150, 2928, 2855, 1256, 1099, 839, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.16 (d, J = 13.4Hz, 1H), 3.89-3.95 (m, 1H), 3.70-3.78 (m, 2H), 3.62 (dd, J = 10.5, 6.3Hz, 1H), 3.55 (dd, J = 5.6, 4.0 Hz, 1H), 3.23 (d, J = 3.9Hz, 1H), 3.14 (ddd, J = 8.7, 6.4, 2.4Hz, 1H), 2.37 (d, J = 11.0 Hz, 1H), 1.23 (br s, 1H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 78.86 (CH), 64.70 (CH_2), 61.66 (CH_2), 61.31 (CH), 52.26 (CH), 51.63 (CH), 25.86 (3 x CH_3), 18.28 (C), -5.37 (CH_3), -5.44 (CH_3);
MS (m/z, relative intensity): 203 (M+-t-Bu, 4), 185 (22), 173 (45), 131 (70), 117 (100).

(1R,4S,5R,6S)-4-(tert-butyl-dimethylsilanyloxymethyl)-3,7-dioxa-bicyclo[4.1.0]heptan-5-ol

Yield: 0.10 g, 41%. R_f = 0.32 (30% EtOAc-hexane).
IR (neat): 3550-3100, 2928, 2856, 1254, 1103, 837, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.18 (dd, J = 13.6, 3.9Hz, 1H), 1.43 (d, J = 6.4Hz, 1H), 3.93 (d, J = 13.5Hz, 1H), 3.75 (dd, J = 5.7, 2.4Hz, 2H), 3.42-3.39 (m, 1H), 3.38-3.36 (m ,1H), 3.28 (dd, J = 4.0, 4.0 Hz, 1H), 2.87 (d, J = 7.0 Hz, 1H),1.62 br s, 1H), 0.86 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 72.51 (CH), 65.32 (CH), 65.07 (CH_2), 63.33 (CH_2), 52.74 (CH), 51.26 (CH), 25.86 (3 x CH_3), 18.22 (C), -5.50 (2 x CH_3);

Example 31

Preparation of 5-benzyloxy-2-hydroxymethyl-tetrahydropyran-3,4-diol



A solution of 4-(tert-butyldimethylsilanyloxymethyl)-3,7-dioxabicyclo[4.1.0]heptan-5-ol (0.06 g, 0.228 mmol) in CH_2Cl_2 (10 ml) was stirred under Argon atmosphere at RT for 15 min. Yttrium triflate (0.048 g, 0.08 mmol) was added and the slurry was stirred for 10 min. Benzyl alcohol (120 µl, 0.912 mmol) was added and the mixture was stirred for 24H. The solvent was removed and the crude product was diluted with EtOAc (20 ml), washed with water (10 ml), saturated aqueous $NaHCO_3$ (5 ml x 2) and brine (5 ml). The organic phase was dried over anhydrous Na_2SO_4. The crude product was purified by flash chromatography using 60% MeOH in EtOAc

Yield: 0.030 g, 51%. R_f = 0.18 (EtOAc).

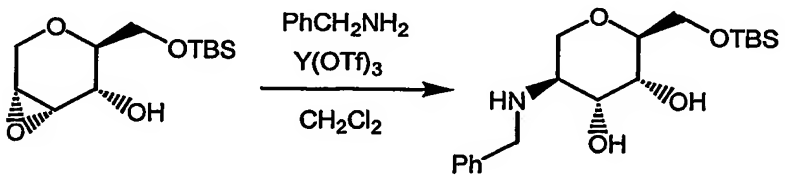
IR (neat): 3600-3100, 3030, 2928, 2856, 1454, 1254, 1103, 837, 698 cm^{-1};

^1H NMR ($CDCl_3$, 400 MHz) δ 7.28-7.33 (m, 5H), 4.48-4.62 (d, 1H, J=12Hz), 4.57 (d, 1H, J=12Hz, 2.3Hz), 4.07-4.12 (m, 2H), 3.93-4.0 (m, 1H), 3.83-3.9 (m, 1H), 3.8-3.85 (m, 1H), 3.75-3.78 (m, 1H), 3.54-3.58 (m, 1H), 3.53-3.54 (m, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.29 (C), 128.90 (2 x CH), 128.27 (CH), 128.09 (2 x CH), 76.50 (CH), 75.01 (CH), 71.66 (CH_2), 68.77 (CH), 67.25 (CH), 64.69 (CH_2), 63.99 (CH_2); MS (m/z, relative intensity): 255 (M^++1, 17), 254 (M^+, 16), 206 (6), 176 (10), 107 (20), 91 (100); HRMS calcd. for $C_{13}H_{18}O_5$: 254.1155; observed: 254.1164.

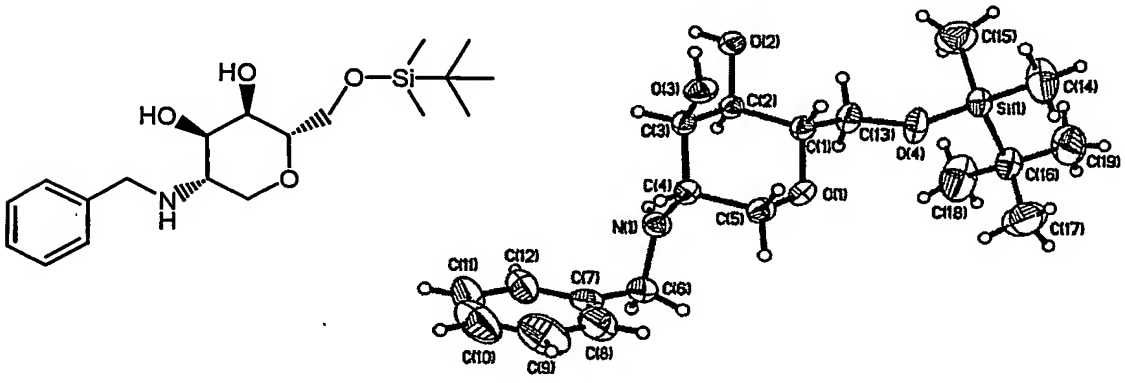
Example 32

Preparation of 5-benzylamino-2-(tert-butyldimethylsilanyloxymethyl)-tetrahydropyran-3,4-diol



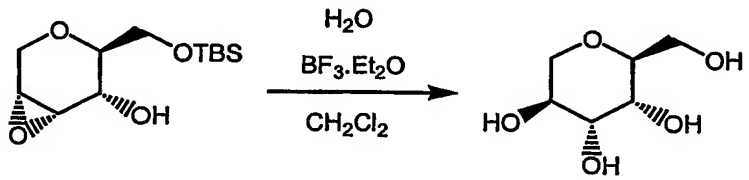
Following the procedure of example 32, the crude product was purified by flash chromatography using 10-20% EtOAc in hexane.

Yield: 0.045 g (53% yield). R_f = 0.18 (1:1 EtOAc-hexane).
IR (neat): 3580, 3500-3200, 2927, 2857, 1464, 1252, 1086, 1062, 838, 780 cm^{-1};
^1H NMR ($CDCl_3$, 200 MHz) δ 7.20-7.30 (m, 5H), 4.00-4.03 (m, 1H), 3.72-3.90 (m, 5H), 3.60-3.70 (m, 2H), 3.48-3.58 (m, 1H), 2.81 (dd, J = 3.5, 1.7Hz, 1H), 0.89 (s, 9H), 0.08 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.88 (C), 128.44 (2 x CH), 128.09 (2 x CH), 127.10 (CH), 73.78 (CH), 69.53(CH), 69.11 (CH), 65.78 (CH_2), 64.78 (CH_2), 56.80 (CH), 51.66 (CH_2), 25.80 (3 x CH_3), 18.16 (C), -5.57 (CH_3), -5.62 (CH_3); MS (m/z, relative intensity): 367 (M^+, 11), 310 (M-*t*-Bu, 22), 148 (22), 91 ($PhCH_2^+$, 100); MS (EI) calcd. for $C_{19}H_{33}NO_4Si$: 367.2179; observed: 367.2171.
X-ray crystal structure of 5-benzylamino-2-(tert-butyldimethylsilanyloxymethyl)-tetrahydropyran-3,4-diol



Example 33

Preparation of 2-hydroxymethyl-tetrahydropyran-3,4,5-triol



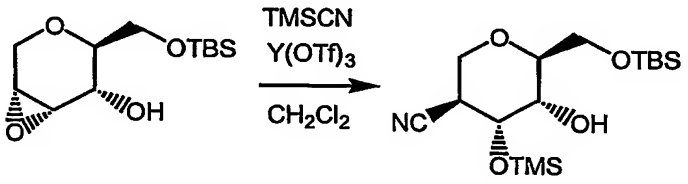
A solution of 4-(tert-butyldimethylsilanyloxymethyl)-3,7-dioxabicyclo[4.1.0]heptan-5-ol (0.06 g, 0.23 mmol) in CH_2Cl_2 (10 ml) was stirred under Argon atmosphere at RT for 15 min. $BF_3.OEt_2$ (1.5 ml, 0.013 mmol) was added followed by water (12 ml, 0.65 mmol). After stirring the mixture for 24h, the solvent was removed and the crude product was purified by flash chromatography using 10% MeOH in EtOAc.

Yield: 0.015 g, 44%. R_f=0.1 (EtOAc).

^1H NMR (D_2O, 400 MHz) δ 4.04 (dd, J = 13.8, 1.5Hz, 1H), 3.84 (dd, J = 11.6, 2.1Hz, 1H), 3.78-3.70 (m, 2H), 3.60 (dd, J = 4.2, 4.2Hz, 1H), 3.50-3.42 (m, 2H), 3.22-3.15 (m, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 75.36, 65.13, 64.44, 61.43, 56.58, 54.99.

Example 34

Preparation of 6-(tert-butyldimethylsilanyloxymethyl)-5-hydroxy-4-trimethylsilanyloxy-tetrahydro-pyran-3-carbonitrile



A solution of 4-(tert-butyldimethylsilanyloxymethyl)-3,7-dioxabicyclo[4.1.0]heptan-5-ol (0.02 g, 0.077 mmol) in CH_2Cl_2 (5 ml) was stirred under Argon atmosphere at RT for 15 min. Yttrium triflate (0.024 g, 0.04 mmol) was added and the slurry was stirred for 10 min. TMSCN (0.022 g, 25 ml, 0.228 mmol) was added and the mixture was stirred for 24H. The solvent was removed and the crude product was diluted with EtOAc (20 ml), washed with water (10 ml), saturated aqueous $NaHCO_3$ (5 ml x 2) and brine (5 ml). The organic phase was dried over anhydrous Na_2SO_4. The crude product was purified by flash chromatography using 10% EtOAc in hexane.

Yield: 0.018 g, 64%. R_f=0.73 (1:1 EtOAc-hexane).

IR (neat): 3550-3100, 2925, 2359, 774 cm^{-1};

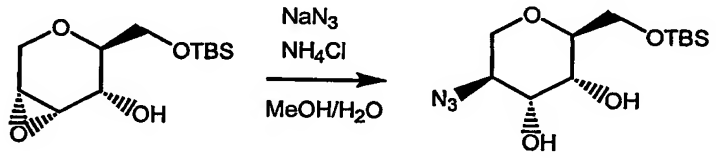
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.00-4.10 (m, 2H), 3.72-3.82 (m, 2H), 3.60-3.70 (m, 1H), 3.42 (dd, J = 4.1, 4.1Hz, 1H), 3.28-3.30 (m, 1H), 3.15-3.20 (m, 1H), 0.87 (s, 9H), 0.17 (s, 9H), 0.03 (s, 6H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 76.02 (CH), 66.50 (CH), 64.95 (CH_2), 63.03 (CH_2), 56.04 (CH), 55.03 (CH), 26.40 (3 x CH_3), 18.90 (C), 0.74 (3 x CH_3), -4.77 (2 x CH_3), -4.89 (2 x CH_3);

MS (m/z, relative intensity): 333 (M^+-CN, 78), 307 (100), 289 (70).

Example 35

Preparation of 5-azido-2-(tert-butyldimethylsilanyloxymethyl)-tetrahydropyran-3,4-diol



A solution of 4-(tert-butyldimethylsilanyloxymethyl)-3,7-dioxabicyclo[4.1.0]heptan-5-ol (0.03 g, 0.12 mmol) in MeOH (4 ml) was treated with water (1 ml) and NaN_3 (0.042 g, 0.65 mmol). The resulting mixture was heated to reflux for 12H. The solvent was removed *in vacuo*. The crude product was diluted with EtOAc (10 ml), washed with water (5 ml x 2), saturated aqueous Na_2CO_3 solution (5 ml) and brine (5 ml). The organic phase was dried over anhydrous Na_2SO_4. The crude product was purified by flash chromatography using 20-25% EtOAc in hexane.

Yield: 0.021 g, 58%. R_f = 0.47 (1:1 EtOAc-hexane).

IR (neat): 3500-3100, 2928, 2108, 1256, 1101, 837, 776 cm^{-1};

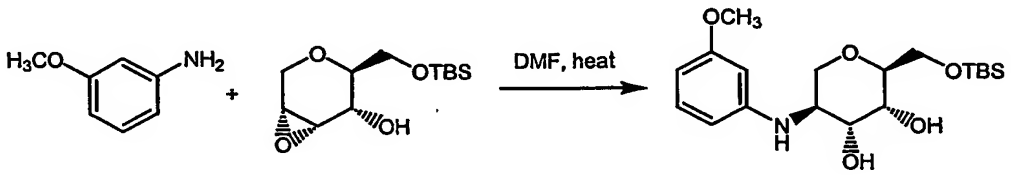
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.40 (d, J = 3.4Hz, 1H), 3.85-3.95 (m, 3H), 3.64-3.82 (m, 3H), 3.49-3.55 (m, 1H), 2.89 (br s, 2H), 0.89 (s, 9H), 0.07 (s, 6H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 77.88, 69.58, 65.91, 64.46, 64.13, 61.94, 26.26 (three CH_3), 18.89, -5.11, -5.12;

MS (m/z, relative intensity): 304 (20, M^++1), 246 (38), 75 (100).

Example 36

Preparation of 2-(tert-butyldimethylsilanyloxymethyl)-5-(3-methoxyphenylamino)-tetrahydropyran-3,4-diol



A solution of 4-(tert-butyldimethylsilanyloxymethyl)-3,7-dioxabicyclo[4.1.0]heptan-5-ol (0.03 g, 0.13 mmol) and m-anisidine (0.08 g, 0.65 mmol) in DMF (4 ml) was heated to reflux for 12H. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography using 15-25% EtOAc in hexane.

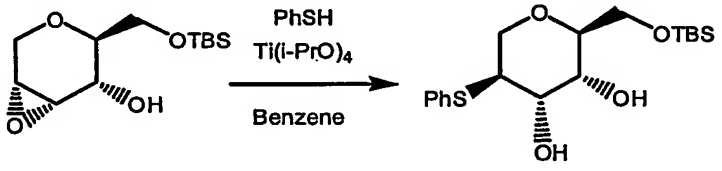
Yield: 0.027 g, 53%. R_f = 0.48 (1:1 EtOAc-hexane).

IR (neat): 3550-3100, 2953, 2928, 2856, 1615, 1254, 1092, 836, 778 cm^{-1};

^1H NMR ($CDCl_3$, 200 MHz) δ 7.00-7.19 (m, 1H), 6.16-6.39 (m, 2H), 3.50-4.20 (m, 8H), 3.75 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H);

Example 37

Preparation of 2-(tert-butyl-dimethylsilanyloxymethyl)-5-phenylsulfanyl-tetrahydropyran-3,4-diol



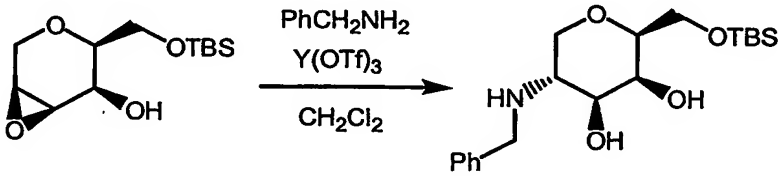
A solution of 4-(tert-butyldimethylsilanyloxymethyl)-3,7-dioxabicyclo[4.1.0]heptan-5-ol (30 mg, 0.115 mmol) in benzene (5 mL) was stirred under Argon atmosphere. Titanium tetraisopropoxide (85 mg, 0.3 mmol) and thiophenol (12 μL, 13 mg, 0.115 mmol) were added sequentially and the resulting mixture was stirred for 24H. The solvent was removed in *vacuo* and the residue was diluted with EtOAc (20 mL), washed with water (5 mLx2), saturated aqueous sodium carbonate solution (5 mL) and brine (5

mL). The organic phase was dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography using 10-20% EtOAc-hexane.

Yield: 0.019 g, 45%. R_f = 0.82 (1:1 EtOAc-hexane).
IR (neat): 3500-3100, 2925, 1090, 775 cm^{-1};
^1H NMR ($CDCl_3$, 200 MHz) δ 7.38-7.42 (m, 2H), 7.24-7.31 (m, 3H), 4.20-3.20 (m, 6H), 2.89-2.86 (m, 2H), 0.89 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H);
MS (EI) calcd. for $C_{18}H_{30}O_4SSi$ 370.1634; observed. 313 (6, M^+-*t*-Bu), 312 (7), 204 (20), 123 (48), 118 (78), 117 (100).

Example 38

Preparation of (2S,3S,4S,5R)-5-benzylamino-2-(tert-butyldimethylsilanyloxymethyl)-tetrahydropyran-3,4-diol



(2S,3S,4S,5R)

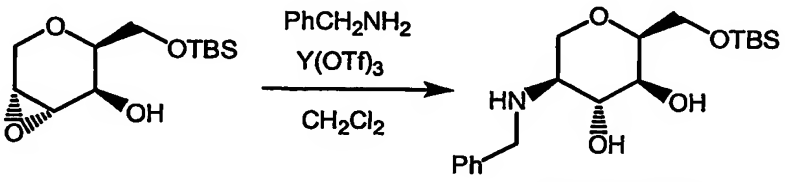
Following the procedure of example 32, the crude product was purified by flash chromatography using 60% EtOAc in hexane.

Yield: 72%. R_f = 0.3 (1:1 EtOAc-hexane).

IR (neat): 3550-3200, 2927, 2855, 1254, 1104, 837, 776, 699 cm^{-1};
^1H NMR ($CDCl_3$, 400 MHz) δ 7.23-7.34 (m, 5H), 3.80-4.05 (m, 7H), 3.86 (br s, 2H), 3.67 (br s, 1H), 3.50 (br s, 1H), 3.12 (br s, 1H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.88 (C), 128.49 (2 x CH), 128.02 (2 x CH), 127.24 (CH), 72.95 (CH), 71.34 (CH), 69.35 (CH_2), 68.23 (CH), 66.29 (CH_2), 58.72 (CH), 52.32 (CH_2), 25.77 (3 x CH_3), 18.18 (C), -5.52 (CH_3), -5.66 (CH_3);
MS (m/z, relative intensity): 367 (M^+, 2), 311 (10), 179 (15), 149 (15), 106 (15), 91 (100);
MS (EI) calcd. for $C_{19}H_{33}NO_4Si$: 367.2179; observed: 367.2184.

Example 39

Preparation of (2S,3S,4R,5S)-5-benzylamino-2-(tert-butyldimethylsilanyloxymethyl)-tetrahydropyran-3,4-diol



(2S,3S,4R,5S)

Following the procedure of example 32, the crude product was purified by column chromatography using 60% EtOAc in hexane.

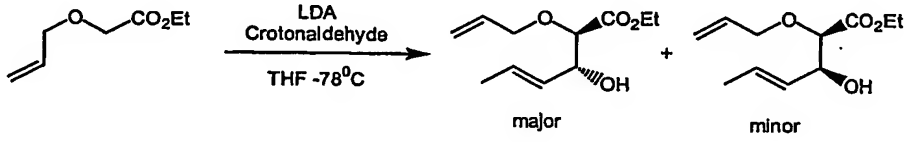
Yield: 63%. R_f=0.33 (1:1 EtOAc-hexane).

IR (neat): 3550-3200, 2927, 2856, 1462, 1254, 1074, 838, 778, 750, 699 cm^{-1};

^1H NMR ($CDCl_3$, 400 MHz) δ 7.24-7.34 (m, 5H), 4.12-4.13 (m, 1H), 4.01 (d, J = 1.4Hz, 1H), 3.90-3.70 (m, 6H), 3.64 (br s, 1H), 2.77 (br s, 1H), 1.24 (br s, 1H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.31 (C), 128.71 (2 x CH), 128.25 (2 x CH), 127.60 (CH), 76.01 (CH), 69.90 (CH), 66.37 (CH), 66.11 (CH_2), 63.24 (CH_2), 57.00 (CH), 51.54 (CH_2), 25.94 (C), 18.37 (3 x CH_3), -5.33 (CH_3), -5.37 (CH_3); MS (m/z, relative intensity): 367 (M^+, 11), 311 (31), 149 (30), 107 (39), 92 (100); MS (EI) calcd. for $C_{19}H_{33}NO_4Si$: 367.2179; observed: 367.2175.

Example 40

Preparation of 2-allyloxy-3-hydroxy-hex-4-enoic acid ethyl ester



A solution of lithium diisopropylamide (LDA) in THF/n-heptane (4.27 mL, 2M, 8.28 mmol) was added to THF (40 mL) at -78°C and the mixture was stirred for 5 min under argon atmosphere. A solution of allyloxyacetic acid ethyl ester (1 g, 6.9 mmol) in THF (10 mL)

was added and stirring was maintained for 5 min. Distilled crotonaldehyde (0.68 mL, 8.28 mmol) was added into the reaction mixture and the resulting solution was allowed to stir for 25 min. The reaction was quenched by the addition of EtOH (5 mL) and the solution was allowed to warm to RT. The solution was diluted with EtOAc (50 mL) and washed with water (10 mL). The organic layer was dried over Na_2SO_4, concentrated in *vacuo* and the residue was purified by flash chromatography with 15% EtOAc-hexane.

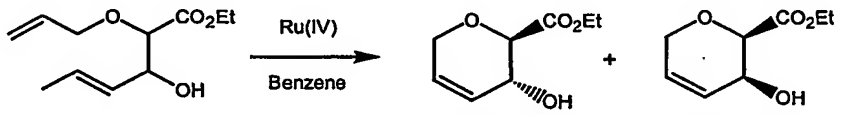
Yield = 0.76 g (51%); R_f= 0.33, 40% EtOAc-hexane

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (t, J = 7.0 Hz, 3H), 1.68 (d, J = 5.8Hz, 3H), 3.85-4.05 (m, 1H), 4.08-4.30 (m, 4H), 5.12-5.38 (m, 2H), 5.40-5.60 (m, 1H), 5.62-6.00 (m, 2H); ^{13}C NMR (125 MHz, ca. 2: 1, for major isomer): δ 170.21 (C), 133.71 (CH), 129.46 (CH), 128.24 (CH), 118.26 (CH_2), 81.06 (CH), 74.92 (CH), 73.44 (CH_2), 60.94 (CH_2), 17.72 (CH_3), 14.19 (CH_3); MS (m/z, relative intensity): 214 (M^+, 3), 196 (36), 155 (58), 127 (21), 71 (100).

HRMS calculated for $C_{11}H_{18}O_4$: 214.1205, found 214.1204.

Example 41

Preparation of cis- and trans-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester



trans (55%) cis (25%)

To a stirred solution of 2-allyloxy-3-hydroxy-hex-4-enoic acid ethyl ester (0.1 g, 0.47 mmol) in dry benzene (20 mL) was added bis-(tricyclohexylphosphine)-benzylidine rutherium (IV) chloride (15 mg, 0.018 mmol) and the mixture was stirred at ambient temperature. The solvent was removed and the residue was purified by flash chromatography with 20-40% EtOAc-hexane.

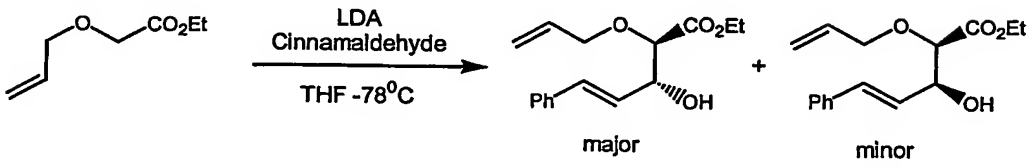
trans-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester

Yield = 56%;

cis-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
Yield = 25%;

Example 42

Preparation of 2-allyloxy-3-hydroxy-5-phenyl-pent-4-enoic acid ethyl ester.



A 2.0M solution of LDA in THF/n-heptane (4.27 mL, 8.28 mmol) was added to THF (40 mL) at -78°C and stirred for 5 min under argon atmosphere. A solution of allyloxyacetic acid ethyl ester (1 g, 6.9 mmol) in THF (20 mL) was added and the reaction mixture was stirred for 25 min. Distilled cinnamaldehyde (1 mL, 8.28 mmol) was added into the reaction mixture and the resulting solution was allowed to stir for 15 min. The reaction was quenched by the addition of EtOH (5 mL) and the solution was allowed to warm to RT. EtOAc (150 mL) was added and the organic layer was washed with water (10 mL), dried over Na_2SO_4, concentrated in *vacuo* and the residue was purified by flash chromatography with 18% EtOAc-hexane.

Yield = 1.37 g (68%); R_f= 0.25, 20% EtOAc-hexane

^{1}H NMR (500 MHz, $CDCl_3$, two isomers): δ 7.20-7.40 (m, 5H), 6.66 (dd, J = 15.5, 6.0 Hz, 1H), 6.30-6.20 (m, 1H), 5.95-5.85 (m, 1H), 5.22 (dd, J = 10.5, 1.0 Hz, 2H), 4.65-4.50 (m, 1H), 4.35-4.18 (m, 2H), 4.15-3.95 (m, 2H), 1.23 (t, J = 7.0 Hz, 3H);

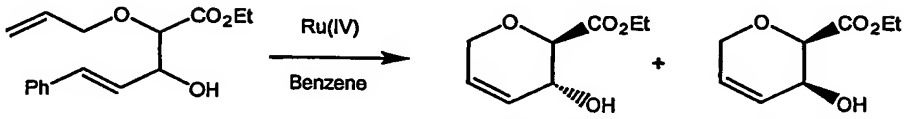
^{13}C NMR (125 MHz, $CDCl_3$, two isomers, ca. 1:1 ratio): δ 170.44 (C), 170.15 (C), 136.34 (C), 136.25 (C), 133.57 (CH), 133.46 (CH), 132.53 (CH), 132.31 (CH), 128.46 (2 x CH) 128.41 (2 x CH) 128.33 (CH), 127.81 (CH), 127.72 (CH), 126.72 (CH), 126.54 (2 x CH), 126.51 (2 x CH), 118.48 (CH_2), 118.36 (CH_2), 81.20 (CH), 80.95 (CH), 73.36 (CH), 72.95 (CH), 71.99 (2 x CH_2), 61.12 (CH_2), 61.02 (CH_2), 14.16 (CH_3), 14.11 (CH_3).

MS (m/z, relative intensity): 276 (M^+, 2), 263 (10), 144 (51), 133 (63), 115 (50), 103 (100);

HRMS calculated for $C_{16}H_{20}O_4$: 276.1362; found 276.1360.

Example 43

Preparation of cis- and trans-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester



trans (49%) cis (26%)

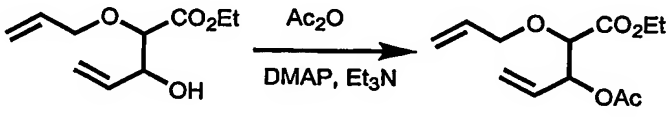
To a stirred solution of 2-allyloxy-3-hydroxy-5-phenyl-pent-4-enoic acid ethyl ester (90 mg, 0.33 mmol) in dry DCM (20 mL) was added bis-(tricyclohexylphosphine)-benzylidine rutherium (IV) chloride (16 mg, 0.018 mmol) and the mixture was stirred at ambient temperature for 30 h. The solvent was removed and the residue was purified by flash chromatography with 20-40% EtOAc-hexane.

trans-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
Yield = 49%;

cis-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester
Yield = 26%;

Example 44

Preparation of 3-acetoxy-2-allyloxy-pent-4-enoic acid ethyl ester



To a solution of 2-allyloxy-3-hydroxy-pent-4-enoic acid ethyl ester (100 mg, 0.5 mmol) and DMAP (30 mg, 0.25 mmol) in CH_2Cl_2-Et_3N (9:1, 10 mL) was added Ac_2O (76 mg, 0.75 mmol). The resulting solution was stirred at ambient temperature for 1H. The solution was diluted with CH_2Cl_2 (40 mL), washed with H_2O (20 mL x 2), dried over

Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography with 20% EtOAc-hexane.

Yield = 119 mg, 99% yield; colorless liquid; R_f = 0.58 in 20% EtOAc-hexane.

IR (neat): 2967, 1747, 1369, 1236, 1028, 932 cm^{-1};

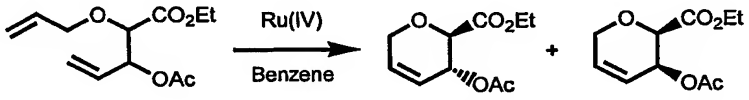
^1H NMR ($CDCl_3$, 400 MHz,): δ 5.80-6.00 (m, 2H), 5.50-5.68 (m, 1H), 5.15-5.40 (m, 4H), 3.90-4.30 (m, 5H), 2.02 (br s, 3H), 1.25 (t, J = 7Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz, 2:1 isomeric forms, *denotes minor isomer): δ 169.64* (C), 169.53 (C), 169.34* (C), 169.29 (C), 133.55* (CH), 133.49 (CH), 132.02* (CH), 131.59 (CH), 119.31 (CH_2), 119.16* (CH_2), 118.27* (CH_2), 118.10 (CH_2), 79.00 (CH), 78.89* (CH), 74.44 (CH), 74.17* (CH), 72.08* (CH_2), 71.89 (CH_2), 61.11 (*CH_2 andCH_2), 20.90 (CH_3), 20.80* (CH_3), 14.12 (CH_3), 14.06* (CH_3);

MS (m/z, relative intensity): 242 (M^+, 19), 200 (22), 169 (41), 142 (13), 110 (100); HRMS calculated for $C_{12}H_{18}O_5$ (M^+): 242.1154; found 242.1160.

Example 45

Preparation of cis- and trans-3-acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester



trans (48%) cis (43%)

To a solution of 3-acetoxy-2-allyloxy-pent-4-enoic acid ethyl ester (300 mg, 1.23 mmol) in CH_2Cl_2 (10 mL) was added bis-(tricyclohexylphosphine)-benzylidine rutherium (IV) chloride (20 mg, 0.024 mmol), the resulting mixture was stirred at ambient temperature for 4H and bis-(tricyclohexylphosphine)-benzylidine rutherium (IV) chloride (20 mg, 0.024 mmol) was added again. The resulting mixture was stirred at ambient temperature for an additional 10 h. The solution was concentrated *in vacuo* and purified by flash chromatography with 15 to 20% EtOAc-hexane.

trans-3-acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester

Yield = 127 mg, 48%; R_f = 0.43 in 20% EtOAc-hexane; IR (neat): 2967, 1747, 1374, 1231, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.96 (dd, J = 10.4, 1.0 Hz, 1H), 5.80-5.85 (m, 1H), 5.44 (br s, 1H), 4.40 (dd, J = 2.4, 17.3Hz, 1H), 4.10-4.25 (m, 4H), 2.03 (s, 3H), 1.23 (t, J = 7.1Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.25 (C), 168.87 (C), 130.63

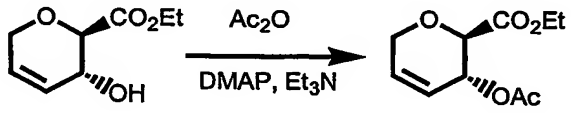
(CH), 122.00 (CH), 74.49 (CH), 65.33 (CH), 63.63 (CH_2), 61.50 (CH_2), 20.96 (CH_3), 14.02 (CH_3); MS (m/z, relative intensity): 215 (M^++1, 6), 213 (M^+-1, 18), 153 (100), 149 (30); HRMS calculated for $C_{10}H_{14}O_5$ (M^+): 214.0841; found 214.0844.

cis-3-acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester

Yield = 117 mg, 43%; R_f = 0.16 in 20% EtOAc-hexane; IR (neat): 2980, 2932, 2831, 1738, 1375, 1234, 1105, 1023 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.95-6.10 (m, 2H), 5.30-5.35 (m, 1H), 4.41 (dd, J = 3.4, 1.6Hz, 1H), 4.15-4.40 (m, 4H), 2.00 (s, 3H), 1.25 (t, J = 7.2Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.12 (C), 167.91 (C), 132.06 (CH), 121.72 (CH), 75.12 (CH), 65.77 (CH_2), 64.87 (CH), 61.33 (CH_2), 20.67 (CH_3), 14.14 (CH_3); MS (m/z, relative intensity): 215 (M^++1, 6), 213 (M^+-1, 18), 153 (100), 149 (30); exact mass calculated for $C_{10}H_{14}O_5$ (M^+): 214.0841; found 214.0839.

Example 46

Preparation of trans-3-acetoxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester

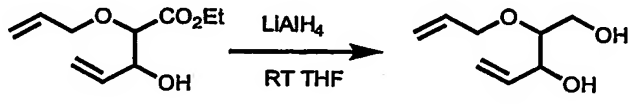


To a solution of trans-3-hydroxy-3,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (70 mg, 0.41 mmol) and DMAP (24 mg, 0.2 mmol) in CH_2Cl_2-Et_3N (9:1, 5 mL) was added Ac_2O (54 mg, 0.53 mmol). The resulting solution was stirred at ambient temperature for 2H. The solution was diluted with CH_2Cl_2 (40 mL), washed with H_2O (20 mL x 2), dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography with 20% EtOAc-hexane.

Yield = 68 mg, 79%; colorless liquid; R_f = 0.16 in 20% EtOAc-hexane;

Example 47

Preparation of 2-allyloxy-pent-4-ene-1,3-diol



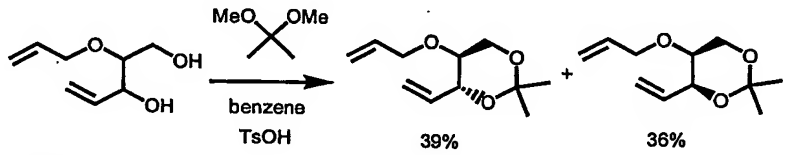
71%

To a solution of 2-allyloxy-3-hydroxy-pent-4-enoic acid ethyl ester (200 mg, 1.00 mmol) in THF (5 mL) was added $LiAlH_4$ (151 mg, 4.00 mmol). The resulting solution was stirred at ambient temperature for 15 min. H_2O (10 mL) was added and the mixture was diluted with EtOAc (50 mL x 2), washed with brine (50 mL), dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography with 50 % EtOAc-hexane

Yield = 112 mg, 71% yield; colorless liquid; R_f= 0.33 in 60% EtOAc-hexane.
IR (neat): 3100-3700, 2880, 1644, 1425, 1055, 996 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.79-5.89 (m, 2H), 5.10-5.31 (m, 4H), 4.04-4.26 (m, 2H), 3.65-3.70 (m, 2H), 3.27-3.30 (m, 1H), 3.01-3.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, *denotes minor isomer): δ 136.98 (CH_2), 134.45 (CH_2), 117.38* (CH), 117.33 (CH), 116.57* (CH), 116.03 (CH), 81.34* (CH_2), 81.11 (CH_2), 72.45 (CH_2), 71.85* (CH), 71.07 (CH), 61.16 (CH); MS (m/z, relative intensity): 127 (M^+-31, 2), 101 (19), 83 (18), 57 (51); exact mass calculated for $C_8H_{14}O_3$ (M^+): 158.0943; found 158.0949.

Example 48

Preparation of cis- and trans-5-allyloxy-2,2-dimethyl-4-vinyl-[1,3]dioxane



To a solution of 2-allyloxy-pent-4-ene-1,3-diol (100 mg, 0.63 mmol) in dry benzene (10ml) was added 2,2-dimethoxypropane (0.39 ml, 3.15 mmol). The resulting solution was stirred for 5 min at ambient temperature, *p*-TsOH (12 mg, 0.06 mmol) was added and stirring was maintained for *ca.* 8H. Aqueous $NaHCO_3$ (10 ml) was added and the mixture was diluted with EtOAc (50 mL), washed with brine (50 mL), dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography with 7% EtOAc-hexane.

trans-5-allyloxy-2,2-dimethyl-4-vinyl-[1,3]dioxane
Yield = 48 mg, 39% yield; colorless liquid; R_f= 0.83 in 15% EtOAc-hexane;
IR (neat): 2992, 1632, 1455, 1375, 1201, 1094 cm^{-1};
^1H NMR ($CDCl_3$, 400 MHz) δ 5.71-5.92 (m, 2H), 5.34 (d, J = 17.3Hz, 1H), 5.12-5.23 (m, 3H), 4.06-4.10 (m, 1H), 3.95-3.97 (m, 2H), 3.90 (J = 11.4, 5.4Hz, 1H), 3.62 (dd, J= 11.3,

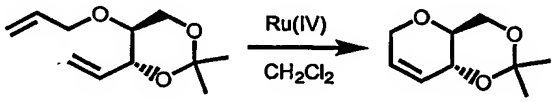
9.1Hz, 1H), 3.18-3.23 (m, 1H), 1.44 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.62 (CH), 135.15 (CH), 118.03 (2 x CH_2), 99.25 (C), 74.85 (CH), 74.43 (CH), 72.04 (CH_2), 63.34 (CH_2), 29.20 (CH_3), 20.04 (CH_3); MS (m/z, relative intensity): 198 (M^+, 2), 183 (15), 142 (19), 84 (90), 83 (38); exact mass calculated for $C_{11}H_{18}O_3$ (M^+): 198.1256; found 198.1255.

cis-5-allyloxy-2,2-dimethyl-4-vinyl-[1,3]dioxane

Yield = 44 mg, 36% yield; colorless liquid; R_f = 0.55 in 15% EtOAc-hexane; IR (neat): 2989, 1647, 1455, 1374, 1196, 1087, 993 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.94-6.03 (m, 1H), 5.81-5.88 (m, 1H), 5.11-5.33 (m, 4H), 4.37 (dd, J= 5.4, 1.5Hz, 1H), 3.90-4.15 (m, 4H), 3.18-3.20 (m, 1H), 1.43 (s, 3H), 1.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.54 (CH), 134.97 (CH), 117.21 (CH_2), 116.98 (CH_2), 98.72 (C), 73.24 (CH), 72.22 (CH), 70.86 (CH_2), 62.09 (CH_2), 29.02 (CH_3), 19.16 (CH_3); MS (m/z, relative intensity): 183 (M^+-15, 8), 142 (5), 84 (100), 83 (38); exact mass calculated for $C_{11}H_{18}O_3$ (M^+): 198.1256; found 198.1254.

Example 49

Preparation of trans-2,2-dimethyl-4,4a,6,8a-tetrahydro-pyrano[3,2-d][1,3]dioxine



84%

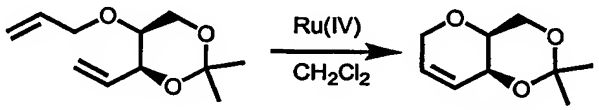
To a solution of trans-5-allyloxy-2,2-dimethyl-4-vinyl-[1,3]dioxane (300 mg, 1.52 mmol) in dry CH_2Cl_2 (10mL) was added bis-(tricyclohexylphosphine)benzylidine ruthenium (IV) chloride (125 mg, 0.15 mmol). The mixture was stirred at ambient temperature for *ca.* 8H, filtered through filter paper and concentrated *in vacuo* to 1 mL. The residue was purified by flash chromatography with 5% EtOAc-hexane

Yield = 84% yield; colorless oil; R_f = 0.48 in 10% EtOAc-hexane; 215 mg,
IR (neat): 3200-3600, 2976, 1747, 1185, 1111, 1024 cm^{-1};
^1H NMR ($CDCl_3$, 400 MHz) δ 5.70-5.79 (m, 1H), 5.66-5.69 (m, 1H), 4.14-4.28 (m, 3H), 3.88 (dd, J = 11.0, 5.0 Hz, 1H), 3.72 (dd, J= 10.4, 10.8Hz, 1H), 3.28-3.34 (m, 1H), 1.49 (s, 3H), 1.39 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 127.19 (CH), 126.80 (CH), 99.65 (C), 71.37 (CH), 67.61 (CH), 66.39 (CH_2), 63.15 (CH_2), 29.24 (CH_3), 19.06 (CH_3);
MS (m/z, relative intensity): 170 (M^+, 5), 169 (55), 97 (91), 83 (54), 70 (100); HRMS calculated for $C_9H_{14}O_3$ (M^+): 170.0943; found 170.0944.

Example 50

Preparation of cis-2,2-dimethyl-4,4a,6,8a-tetrahydro-pyrano[3,2-d][1,3]dioxine



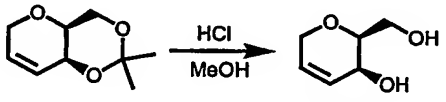
78%

To a solution of cis-5-allyloxy-2,2-dimethyl-4-vinyl-[1,3]dioxane (300 mg, 1.52 mmol) in dry CH_2Cl_2 (10mL) was added bis-(tricyclohexylphosphine)benzylidine ruthenium (IV) chloride (120 mg, 0.14 mmol). The mixture was stirred at ambient temperature for *ca.* 8H, filtered through filter paper and concentrated *in vacuo* to 1 mL. The residue was purified by flash chromatography with 15% EtOAc-hexane

Yield = 198 mg, 78%; colorless oil; R_f= 0.15 in 10% EtOAc-hexane;
IR (neat): 3200-3600, 2976, 1747, 1185, 1111, 1024 cm^{-1};
^1H NMR ($CDCl_3$, 400 MHz) δ 6.04-6.08 (m, 1H), 5.84-5.89 (m, 1H), 4.25-4.35 (m, 1H), 4.09-4.15 (m, 3H), 3.88 (dd, J= 12.8, 2.8Hz, 1H), 3.40 (dd, J= 6.0, 2.8Hz, 1H), 1.47 (s, 3H), 1.44 (s, 3H);
^{13}C NMR ($CDCl_3$, 100 MHz) δ 132.03 (CH), 123.20 (CH), 98.99 (C), 69.50 (CH), 65.29 (CH_2), 62.99 (CH_2), 61.57 (CH), 28.19 (CH_3), 19.82 (CH_3);
MS (m/z, relative intensity): 170 (M^+, 5), 169 (55), 97 (91), 83 (54), 70 (100); HRMS calculated for $C_9H_{14}O_3$ (M^+): 170.0943; found 170.0939.

Example 51

Preparation of cis-2-hydroxymethyl-3,6-dihydro-2H-pyran-3-ol



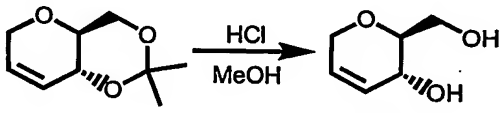
78%

To a solution of cis-5-allyloxy-2,2-dimethyl-4-vinyl-[1,3]dioxane (50 mg, 0.29 mmol) in MeOH (5 mL) was added a solution of methanolic HCl (0.5 mL, prepared from 0.5 mL conc. HCl in 30 mL of MeOH). The mixture was stirred for 30 min at ambient temperature. Aqueous saturated $NaHCO_3$ (5 mL) was added and the mixture was diluted with EtOAc (50 mL). The organic layer was washed with saturated $NaHCO_3$ (30 mL). The aqueous layer was washed with EtOAc (30 mL x 2). The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo*, and the residue was purified by flash chromatography with 100% EtOAc

Yield = 29 mg, 78% yield; colorless oil; R_f = 0.25 in EtOAc;

Example 52

Preparation of trans-2-hydroxymethyl-3,6-dihydro-2H-pyran-3-ol



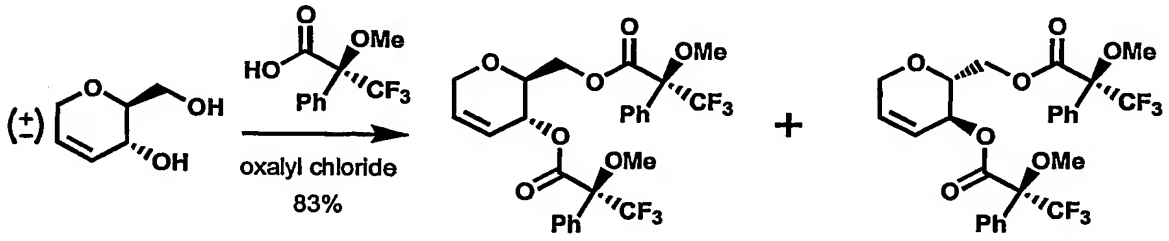
83%

To a solution of trans-5-allyloxy-2,2-dimethyl-4-vinyl-[1,3]dioxane (48 mg, 0.28 mmol) in MeOH (5 mL) was added a solution of methanolic HCl (0.5 mL, prepared from 0.5 mL conc. HCl in 30 mL of MeOH). The mixture was stirred for 30 min at ambient temperature. Aqueous saturated $NaHCO_3$ (5 mL) was added and the mixture was diluted with EtOAc (50 mL). The organic layer was washed with saturated $NaHCO_3$ (30 mL). The aqueous layer was washed with EtOAc (30 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated *in vacuo*, and the residue was purified by flash chromatography with 100% EtOAc.

Yield = 30 mg, 83% yield; colorless oil; R_f = 0.20 in 100% EtOAc;

Example 53

Preparation of trans-2-hydroxymethyl-3,6-dihydro-2H-pyran-3-ol bis-(S)-Mosher ester

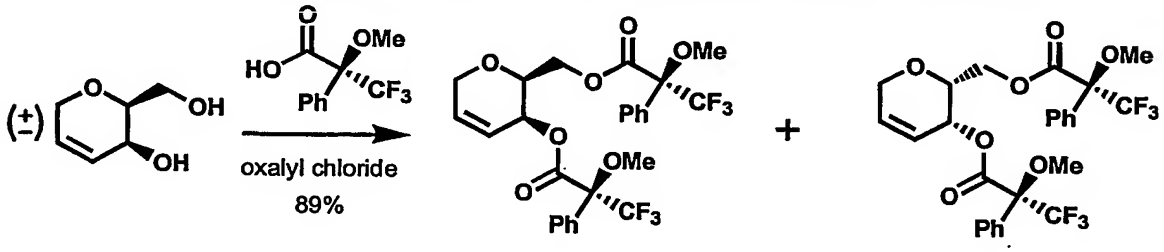


To a solution of (S)-Mosher acid (108 mg, 0.46 mmol) in dry benzene (1 mL) were added sequentially oxalyl chloride (0.5 mL) and DMF (1 drop). The solution was stirred for 5 min at ambient temperature, concentrated *in vacuo* and diluted with dry CH_2Cl_2 (3 mL). Et_3N (0.13 mL, 0.92 mmol), DMAP (11 mg, 0.08 mmol) and a solution of racemic trans-2-hydroxymethyl-3,6-dihydro-2H-pyran-3-ol (22 mg, 0.17 mmol) in CH_2Cl_2 (2 mL) were added sequentially and the solution was stirred for 24H. H_2O (2 ml) was added and the mixture was diluted with CH_2Cl_2 (50 mL) and washed with brine (30 mL). The aqueous layer was washed with CH_2Cl_2 (50 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated *in vacuo*, and the residue was purified by flash chromatography with 10% EtOAc-hexane

Yield = 79 mg, 83%; colorless oil; R_f = 0.69 in 20% EtOAc-hexane.
IR (neat): 2952, 2849, 1752, 1650, 1495, 1271, 1170, 1122, 1023, 765 cm^{-1};
^1H NMR ($CDCl_3$, 400 MHz, two isomers): δ 7.45-7.51 (m, 8H), 7.31-7.41 (m, 12H), 6.10-6.15 (m, 2H), 6.07-6.08 (m, 2H), 5.14-5.16 (m, 1H), 5.07-5.09 (m, 1H), 4.52-4.56 (m, 1H), 4.25-4.40 (m, 4H), 4.05-4.18 (m, 3H), 3.89-3.98 (m, 2H), 3.52-3.59 (m, 9H), 3.46-3.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, two isomers): δ 166.64 (C), 166.61 (C), 166.53 (C), 166.41 (C), 134.34 (CH), 134.14 (CH), 132.57 (C), 132.44 (C), 132.34 (C), 132.00 (C), 130.14 (2 x CH), 130.10 (four of CH), 129.59 (C), 128.87 (six of CH and 2 x C), 128.72 (two C), 127.97 (2 x CH), 127.71 (four of CH), 127.68 (two C), 127.57 (2 x CH), 126.96 (C), 121.02 (CH), 120.81 (CH), 73.44 (CH), 73.04 (CH), 67.03 (CH), 67.01 (CH), 65.91 (CH_2), 65.86 (CH_2), 64.71 (CH_2), 64.50 (CH_2), 55.86 (2 x CH_3), 55.70 (2 x CH_3); MS (m/z, relative intensity): 562 (M^+,2), 342 (10), 128 (23), 91 (100);

Example 54

Preparation of cis-2-hydroxymethyl-3,6-dihydro-2H-pyran-3-ol bis-(S)-Mosher ester

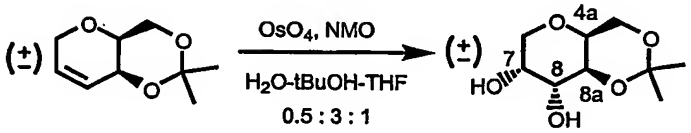


To a solution of (S)-Mosher acid (108 mg, 0.46 mmol) in dry benzene (1 mL) were added sequentially oxalyl chloride (0.5 mL) and DMF (1 drop). The solution was stirred for 5 min at ambient temperature, concentrated in vacuo and diluted with dry CH_2Cl_2 (3 mL). Et_3N (0.13 mL, 0.92 mmol), DMAP (11 mg, 0.08 mmol), a solution of racemic cis-2-hydroxymethyl-3,6-dihydro-2H-pyran-3-ol (20 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) were added sequentially and the solution was stirred for 24H. H_2O (2 ml) was added and the mixture was diluted with CH_2Cl_2 (50 mL) and washed with brine (30 mL). The aqueous layer was washed with CH_2Cl_2 (50 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated *in vacuo*, and the residue was purified by flash chromatography with 10% EtOAc-hexane

Yield = 80 mg, 89%; colorless oil; R_f = 0.49 in 20% EtOAc-hexane;
IR (neat): 2952, 2850, 1750, 1657, 1452, 1270, 1170, 1122, 1019, 721 cm^{-1};
^1H NMR ($CDCl_3$, 400 MHz, two isomers): δ 7.58-7.45 (m, 8H), 7.40-7.30 (m, 12H), 6.00-5.90 (m, 2H), 5.85-5.80 (m, 1H), 5.78-5.70 (m, 1H), 5.48-5.38 (m, 2H), 4.44-4.35 (m, 2H), 4.20-4.03 (m, 6H), 3.82-3.72 (m, 1H), 3.70-3.65 (m, 1H), 3.555-3.45 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz, two isomers): δ 166.35 (C), 166.20 (C), 166.14 (C), 165.81 (C), 132.11 (C), 132.07 (C), 132.01 (C), 131.66 (C), 130.64 (2 x CH), 130.61 (2 x CH), 129.81 (2 x CH), 129.77 (2 x CH), 129.65 (2 x CH), 129.63 (2 x CH), 128.59 (2 x CH and one C), 128.53 (2 x CH and one C), 128.19 (2 x CH and 2 x C), 127.41 (2 x CH), 127.29 (2 x C), 126.97 (2 x C), 123.03 (two CH), 122.65 (2 x CH), 73.09 (CH), 73.01 (CH), 67.40 (CH), 67.19 (CH), 65.36 (CH_2), 65.01 (CH_2), 64.40 (CH_2), 63.97 (CH_2), 55.48 (2 x CH_3), 55.38 (2 x CH_3); MS (m/z, relative intensity): 561 (M^+-1, 5), 345 (9), 128 (22), 105 (52), 95 (70), 91 (100);

Example 55

Preparation of racemic (4aS,7R,8R,8aS)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol



70%

To a solution of 2,2-dimethyl-4,4a,6,8a-tetrahydro-pyrano[3,2-d][1,3]dioxine (50 mg, 0.29 mmol) in 4.5 mL of THF-tert-BuOH-H_2O (1:3:0.5) was added NMO (45 mg, 0.32 mmol) and the solution was stirred for 5 min at ambient temperature. OsO_4 (15 μL, 25 wt% in tert-BuOH) was added and the solution was stirred at ambient temperature for 4 days. Sodiumhydrosulphite (0.2 g), Florisil (2.0 g) and H_2O (5 ml) were added and the mixture was stirred for 30 minutes, wash with acetone (100mL), filtered through filter paper and extracted with EtOAc (80 mL x 2). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, concentrated *in vacuo*, and the residue was purified by flash chromatography with 60% EtOAc-hexane.

Yield = 41 mg, 70%; colorless oil; R_f = 0.13 in 70% EtOAc-hexane;

IR (neat) 3550-3100, 2929, 1392, 1081 cm^{-1};

^1H NMR (C_6D_6, 400 MHz) δ 4.02-4.12 (m, 1H), 3.90-3.95 (m, 2H), 3.71-3.83 (m, 2H), , 3.50-3.60 (m, 2H), 3.26 (br s, 1H), 1.48 (s, 3H), 1.15 (s, 3H);

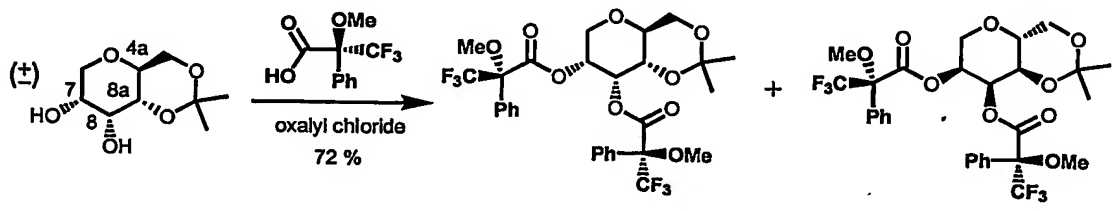
^{13}C NMR (C_6D_6, 100 MHz) δ 99.02 (C), 70.55 (CH), 70.34 (CH), 67.05 (CH), 66.08 (CH_2), 65.61 (CH), 63.83 (CH_2), 30.27 (CH_3), 19.35 (CH_3);

MS (m/z, relative intensity): 204 (M^+, 5), 170 (18), 146 (12), 103 (42), 91 (91), 43 (100);

HRMS calculated for $C_9H_{16}O_5$ (M^+): 204.0998; found 204.0993.

Example 56

Preparation of the bis-(S)-Mosher ester of racemic (4aS,7R,8R,8aR)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol

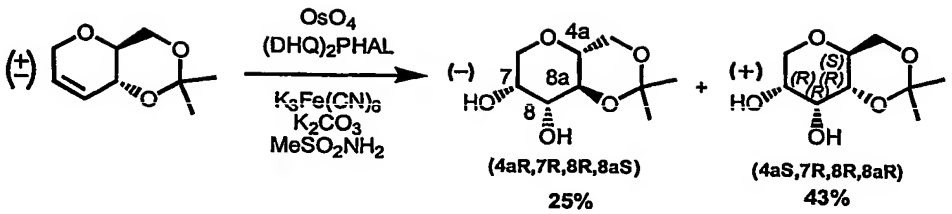


To a solution of (S)-Mosher acid (130 mg, 0.64 mmol) in dry benzene (1 mL) were sequentially added oxalyl chloride (0.5 mL) and DMF (1 drop). The solution was stirred for 5 min at ambient temperature, concentrated in vacuo and diluted with dry CH_2Cl_2 (3 mL). Et_3N (0.45 mL, 3.20 mmol), DMAP (40 mg, 0.32 mmol) and a solution of 2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol (130 mg, 0.64 mmol) in CH_2Cl_2 (2 mL) were added sequentially and the solution was stirred for 24H. H_2O (2 ml) was added, the mixture was diluted with CH_2Cl_2 (50 mL) and washed with brine (30 mL). The aqueous layer was washed with CH_2Cl_2 (50 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated *in vacuo*, and the residue was purified by flash chromatography with 5% EtOAc-hexane

Yield = 314 mg, 72%; colorless oil; R_f = 0.68 in 10% EtOAc-hexane; IR (neat): 3100-3650, 2926, 1377, 1321, 1156, 1108, 1062 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, two isomers) δ 7.55-7.50 (m, 6H), 7.47-7.28 (m, 12H), 7.19-7.15 (m, 2H), 5.57-5.31 (m, 4H), 4.10-3.20 (m, 12H), 3.61 (s, 3H), 3.47 (s, 3H), 3.45 (s, 3H), 3.27 (s, 3H), 1.38 (s, 3H), 1.36 (s, 6H), 1.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, two isomers) δ 166.06 (C), 165.78 (C), 165.34 (C), 165.26 (C), 132.19 (C), 132.12 (C), 131.82 (C), 131.50 (C), 129.61 (CH), 129.52 (2 x CH), 129.51 (C), 129.46 (CH), 128.29 (six of CH), 128.22 (3 x CH), 128.13 (3 x CH), 127.54 (2 x C), 127.46 (2 x CH), 127.36 (C), 127.09 (2 x CH), 124.56 (C), 124.50 (C), 121.69 (C), 121.62 (C), 99.92 (2 x C), 73.26 (2 x CH), 72.53 (CH), 71.90 (CH), 71.81 (CH), 71.76 (CH), 69.13 (CH), 68.73 (CH), 68.32 (CH_2), 68.05 (CH_2), 61.88 (CH_2), 60.30 (CH_2), 55.55 (CH_3), 55.49 (CH_3), 55.26 (CH_3), 55.03 (CH_3), 28.96 (CH_3), 28.91 (CH_3), 18.77 (CH_3), 18.39 (CH_3); MS (m/z, relative intensity): 636 (M^+, 2), 417 (3), 376 (15), 283 (39), 189 (100), 105 (22), 95 (51); HRMS calculated for $C_{29}H_{30}O_9F_6$ (M^+): 636.1890; found 636.1900.

Example 57

Preparation of the (-)-(4aR,7R,8R,8aS)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol and (+)-(4aS,7R,8R,8aR)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol



To a solution of racemic trans-2,2-dimethyl-4,4a,6,8a-tetrahydro-pyrano[3,2-d][1,3]dioxine (70 mg, 0.41 mmol) in H_2O-tert-BuOH (1:1, 4 mL), were added sequentially $K_3Fe(CN)_6$ (430 mg, 1.24 mmol), K_2CO_3 (180 mg, 1.24 mmol), $MeSO_2NH_2$ (75 mg, 0.82 mmol) and $(DHQ)_2PHAL$ (31 mg, 0.04 mmol) at 0°C. The solution was stirred for 5 min, OsO_4 (10 *u*L, 25 wt% in tert-BuOH) was added and the mixture was stirred for 64H at ambient temperature. Na_2SO_3 (100 mg) was added and the mixture was stirred for 30 min, filtered through filter paper and extracted with EtOAc-H_2O (4:1 *v/v*, 100 mL x 2). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, concentrated *in vacuo*, and the residue was purified by flash chromatography with 100% EtOAc.

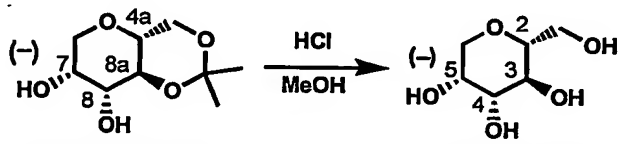
(-)-(4aR,7R,8R,8aS)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol
Yield = 21 mg, 25%; colorless oil; R_f = 0.30 in 100% EtOAc;
IR (neat): 3200-3600, 2976, 1747, 1185, 1111, 1024 cm^{-1};
^1H NMR (C_6D_6, 500 MHz) δ 3.97 (dd, J = 9.5Hz, 1H), 3.90-3.82 (m, 2H), 3.74 (dd, J = 10.5, 10.5Hz, 1H), 3.56 (br s, 1H), 3.41 (dd, J = 9.5, 3.5Hz, 1H), 3.04-2.98 (m, 2H), 2.84 (br s, 2 OH), 1.45 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz) δ 99.86 (C), 72.69 (CH), 72.15 (CH), 72.02 (CH), 70.36 (CH_2), 69.73 (CH), 62.30 (CH_2), 29.47 (CH_3), 19.12 (CH_3); MS (m/z, relative intensity): 204 (M^+, 5), 186 (12), 98 (28), 73 (100); exact mass calculated for $C_9H_{16}O_5$ (M^+): 204.0998; found 204.0991.

(+)-(4aS,7R,8R,8aR)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol
Yield = 36 mg, 43%; colorless oil; R_f = 0.51 in 100% EtOAc;
IR (neat): 3200-3600, 2976, 1747, 1185, 1111, 1024 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 3.88 (dd, J = 10.0, 4.5Hz, 1H), 3.85 (br s, 1H), 3.73 (dd, J = 10.5, 5.5Hz, 1H), 3.60-3.48 (m, 3H), 3.37 (dd, J = 10.5, 10.5Hz, 1H), 3.21 (d, J = 10.5Hz, 1H), 1.36 (s, 3H), 1.15 (3, 3H); ^{13}C NMR (C_6D_6, 125 MHz) δ 99.32 (C), 72.24 (CH), 68.96 (CH), 67.40 (CH), 67.29 (CH_2), 66.62 (CH), 62.87 (CH_2), 29.19 (CH_3), 19.10 (CH_3); MS (m/z, relative intensity):

204 (M^+, 3), 186 (8), 158 (4), 115 (10), 98 (26), 73 (100); exact mass calculated for $C_9H_{16}O_5$ (M^+): 204.0998; found 204.0991.

Example 58

Preparation of (-)-(2R,3S,4R,5R)-2-hydroxymethyl-tetrahydro-pyran-3,4,5-triol



(4aR,7R,8R,8aS) (2R,3S,4R,5R)

83 %

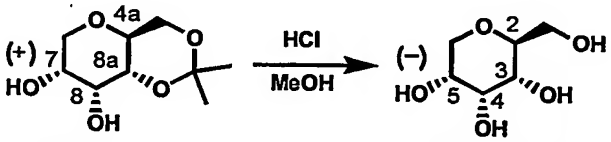
To a solution of (-)-(4aR,7R,8R,8aS)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol (42 mg, 0.21 mmol) in MeOH (2 mL) was added a solution of methanolic HCl (0.6 mL, prepared from 0.5 mL conc. HCl in 30 mL of MeOH). The solution was stirred for 1H at ambient temperature and concentrated *in vacuo*.

Yield = 28 mg, 83% yield;

IR (neat): 3000-4900, 2927, 1421, 1274, 1067cm^{-1}; ^1H NMR (D_2O, 500 MHz) δ 3.86 (br s, 1H), 3.80 (dd, J = 12.5, 1.5Hz, 1H), 3.77 (dd, J = 12.5, 2.5Hz, 1H), 3.58-3.44 (m, 4H), 3.20-3.16 (m, 1H); ^{13}C NMR (D_2O, 125 MHz) δ 80.68 (CH), 73.67 (CH), 70.00 (CH_2), 69.24 (CH), 67.45 (CH), 61.40 (CH_2); MS (m/z, relative intensity): 164 (M^+, 5), 145 (32), 128 (10), 102 (71), 73 (100); exact mass calculated for $C_6H_{12}O_5$ (M^+): 164.0685; found 164.0690.

Example 59

Preparation of (-)-(2S,3R,4R,5R)-2-hydroxymethyl-tetrahydro-pyran-3,4,5-triol



(4aS,7R,8R,8aR) (2S,3R,4R,5R)

74%

To a solution of (+)-(4aS,7R,8R,8aR)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol (28 mg, 0.14 mmol) in MeOH (2 mL) was added a solution of

methanolic HCl (0.4 mL, prepared from 0.5 mL conc. HCl in 30 mL of MeOH). The solution was stirred for 1H at ambient temperature and concentrated *in vacuo*.

Yield = 17 mg, 74% yield;

IR (neat): 3000-3600, 2938, 1418, 1231, 1057, 911, 773 cm^{-1};

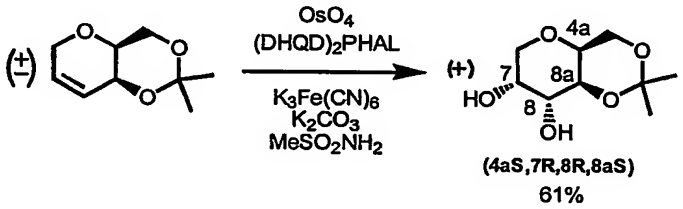
^1H NMR (D_2O, 500 MHz) δ 4.04 (br s, 1H), 3.75 (d, J = 12.0 Hz, 1H), 3.71-3.66 (m, 1H), 3.65-3.60 (m, 1H), 3.57-3.52 (m, 1H), 3.46-3.38 (m, 3H);

^{13}C NMR (D_2O, 125 MHz) δ 75.07 (CH), 70.56 (CH), 67.07 (CH), 66.78 (CH), 64.48 (CH_2), 61.34 (CH_2);

MS (m/z, relative intensity): 164 (M^+, 4), 146 (13), 128 (10), 103 (40), 102 (52), 98 (32), 73 (100); exact mass calculated for $C_6H_{12}O_5$ (M^+): 164.0685; found 164.0688.

Example 60

Preparation of (+)-(4aS,7R,8R,8aS)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol



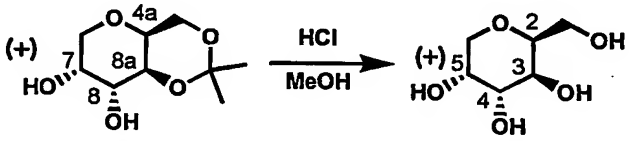
To a solution of racemic cis-2,2-dimethyl-4,4a,6,8a-tetrahydro-pyrano[3,2-d][1,3]dioxine (100 mg. 0.58 mmol) in 4 mL of H_2O-tert-BuOH (1:1), were added sequentially $K_3Fe(CN)_6$ (580 mg, 1.76 mmol), K_2CO_3 (243 mg, 1.76 mmol), $MeSO_2NH_2$ (110 mg, 1.16 mmol) and $(DHQD)_2PHAL$ (60 mg, 0.08 mmol) at 0°C. The solution was stirred for 5 min and OsO_4 (10 μL, 25 wt% in tert-BuOH) was added and stirring was maintained for 62H at ambient temperature. Na_2SO_3 (100 mg) was added and the mixture was stirred for 30 min, filtered through filter paper and extracted with EtOAc-H_2O (4:1 *v/v*, 100 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography with 100% EtOAc.

Yield = 72 mg, 61%; colorless oil; R_f = 0.35 in 100% EtOAc;

IR (neat) 3600-3100, 2987, 2920, 1382, 1086 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 4.02-3.95 (m, 1H), 3.90-3.82 (m, 3H), 3.63 (dd, J = 10.6, 5.4Hz, 1H), 3.54 (dd, 12.7, 2.2Hz, 1H), 3.47 (dd, J = 10.6, 10.6Hz, 1H), 3.18 (br s, 1H), 1.47 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 98.29 (C), 69.70 (CH), 69.56 (CH), 66.30 (CH), 65.21 (CH_2), 64.80 (CH), 63.08 (CH_2), 29.57 (CH_3), 18.62 (CH_3); MS (m/z, relative intensity): 204 (M+, 5), 170 (18), 146 (12), 103 (42), 91 (91), 59 (40), 57 (40), 43 (100); exact mass calculated for $C_9H_{16}O_5$ (M^+): 204.0998; found 204.0993.

Example 61

Preparation of (+)-(2S,3S,4R,5R)-2-hydroxymethyl-tetrahydro-pyran-3,4,5-triol



(4aS,7R,8R,8aS) (2S,3S,4R,5R)

76%

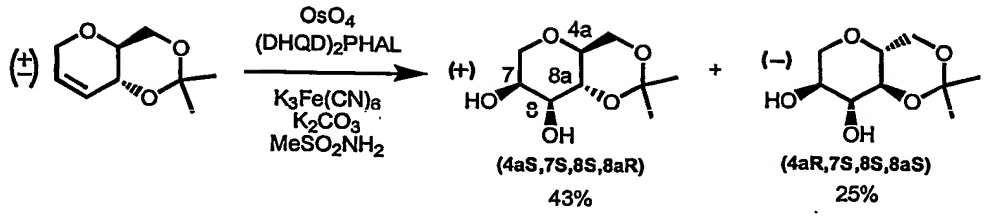
To a solution of (+)-(4aS,7R,8R,8aS)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol (36 mg, 0.18 mmol) in MeOH (2 mL) was added a solution of methanolic HCl (0.5 mL, prepared from 0.5 mL conc. HCl in 30 mL of MeOH). The solution was stirred for 1H at ambient temperature and concentrated *in vacuo*.

Yield = 15 mg, 76%;

IR (neat): 3000-3600, 2944, 2913, 2891, 1460, 1380, 1296, 1114, 1024 cm^{-1}; ^1H NMR (D_2O, 400 MHz) δ 4.00-3.90 (m, 2H), 3.76-3.73 (m, 1H), 3.72-3.65 (m, 2H), 3.62-3.60 (m, 2H), 3.45 (dd, J= 10.6Hz, 1H); ^{13} C NMR (D_2O, 100 MHz) δ 75.34 (CH), 69.86 (CH), 69.72 (CH), 65.36 (CH_2), 64.57 (CH), 61.40 (CH_2); MS (m/z, relative intensity): 164 (M^+, 2), 146 (13), 128 (11), 103 (33), 102 (26), 74 (31), 73 (72), 70 (100); exact mass calculated for $C_6H_{12}O_5$ (M^+): 164.0685; found 164.0680.

Example 62

Preparation of (+)-(4aS,7S,8S,8aR)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol and (-)-(4aR,7S,8S,8aS)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol



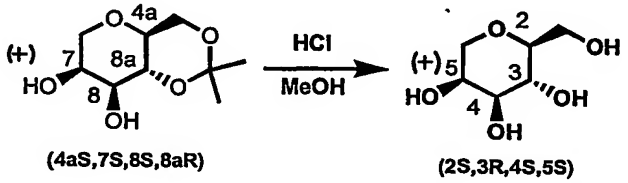
To a solution of racemic trans-2,2-dimethyl-4,4a,6,8a-tetrahydro-pyrano[3,2-d][1,3]dioxine (75 mg, 0.44 mmol) in 4 mL of H_2O-tert-BuOH (1:1), were added sequentially $K_3Fe(CN)_6$ (435 mg, 1.32 mmol), K_2CO_3 (182 mg, 1.32 mmol), $MeSO_2NH_2$ (76 mg, 0.88 mmol) and $(DHQD)_2PHAL$ (31 mg, 0.04 mmol) at 0°C. The solution was stirred for 5 min, OsO_4 (10 μL, 25%wt in tert-BuOH) was added and the mixture was stirred for 56H at ambient temperature. Na_2SO_3 (100 mg) was added and the mixture was stirred for 30 min, filtered through filter paper and extracted with EtOAc-H_2O (4:1 *v/v*, 100 mL x 2). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, concentrated *in vacuo* and the residue was purified by flash chromatography with 100% EtOAc.

(+)-(4aS,7S,8S,8aR)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol
Yield = 27 mg, 30%; colorless oil; R_f = 0.29 in 100% EtOAc;
IR (neat): 3150-3600, 2965, 1749, 1901, 1124, 1096 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 4.02 (dd, J = 9.5, 9.5Hz, 1H), 3.90-3.86 (m, 2H), 3.77 (dd, J = 10.5, 10.5Hz, 1H), 3.62 (br s, 1H), 3.46 (dd, J = 9.5, 3.0 Hz, 1H), 3.19 (br. s, 2H), 3.20-3.00 (m, 2H), 1.47 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz) δ 99.92 (C), 72.77 (CH), 72.13 (CH), 72.02 (CH), 70.47(CH_2), 69.82 (CH), 62.28 (CH_2), 29.48 (CH_3), 19.15 (CH_3); MS (m/z, relative intensity): 204 (M^+, 1), 186 (19), 170 (17), 128 (34), 105 (39), 97 (91), 84 (100); exact mass calculated for $C_9H_{16}O_5$ (M^+): 204.0998; found 204.0999.

(-)-(4aR,7S,8S,8aS)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol
Yield = 39 mg, 43%; colorless oil; R_f = 0.41 in 100% EtOAc;
IR (neat): 3200-3600, 2976, 1747, 1185, 1111, 1024 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 3.88 (dd, J = 11.5, 4.5Hz, 1H), 3.85 (br s, 1H), 3.74 (dd, J = 11.0, 6.0 Hz, 1H), 3.60-3.50 (m, 3H), 3.72 (dd, J = 11.0, 11.0 Hz, 1H), 3.21 (dd, J = 9.0, 2.0 Hz, 1H), 1.37 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz) δ 99.32 (C), 72.24 (CH), 68.96 (CH), 67.40 (CH), 67.29 (CH_2), 66.62 (CH), 62.87 (CH_2), 29.20 (CH_3), 19.09 (CH_3); MS (m/z, relative intensity): 186 (M^+-18, 5), 170 (6), 128 (39), 105 (42), 97 (91), 84 (100); exact mass calculated for $C_9H_{16}O_5$ (M^+): 204.0998; found 204.0989

Example 63

Preparation of (+)-(2S,3R,4S,5S)-2-hydroxymethyl-tetrahydro-pyran-3,4,5-triol



(4aS,7S,8S,8aR) (2S,3R,4S,5S)

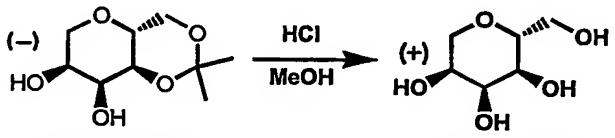
85%

To a solution of (+)-(4aS,7S,8S,8aR)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol (24 mg, 0.12 mmol) in MeOH (2 mL) was added a solution of methanolic HCl (0.4 mL, prepared from 0.5 mL conc. HCl in 30 mL of MeOH). The solution was stirred for 1H at ambient temperature and concentrated *in vacuo*.

Yield = 17 mg, 85%; IR (neat): 3000-4900, 2927, 1421, 1274, 1067 cm^{-1}; ^1H NMR (D_2O, 500 MHz) δ 3.86 (br s, 1H), 3.81 (dd, J = 12.5, 1.5Hz, 1H), 3.78 (dd, J = 12.5, 2.5Hz, 1H), 3.57 (dd, J = 12.5, 6.5Hz, 1H), 3.55-3.49 (m, 2H), 3.46 (d, J = 9.5Hz, 1H), 3.18 (ddd, J = 9.5, 6.5, 2.5Hz, 1H); ^{13}C NMR (H_2O, 125 MHz) δ 80.67 (CH), 73.99 (CH), 69.99 (CH_2), 69.22 (CH), 67.45 (CH), 61.39 (CH_2); MS (m/z, relative intensity): 164 (M^+, 3), 146 (12), 128 (7), 102 (34), 98 (16), 73 (100); exact mass calculated for $C_6H_{12}O_5$ (M^+): 164.0685; found 164.0692.

Example 64

Preparation of (+)-(2R,3S,4S,5S)-2-hydroxymethyl-tetrahydro-pyran-3,4,5-triol



(4aR,7S,8S,8aS) (2R,3S,4S,5S)

82%

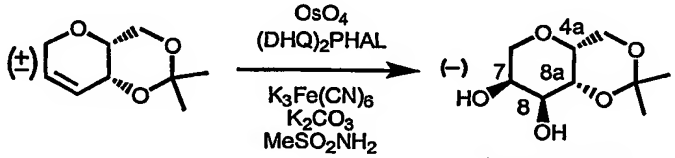
To a solution of (-)-(4aR,7S,8S,8aS)-2,2-dimethyl-hexahydropyrano[3,2-d][1,3]dioxine-7,8-diol (20 mg, 0.09 mmol) in MeOH (2 mL) was added a solution of methanolic HCl (0.5 mL, prepared from 0.5 mL conc. HCl in 30 mL of MeOH). The solution was stirred for 1H at ambient temperature and concentrated *in vacuo*.

Yield = 12 mg, 74%;

IR (neat): 3000-3600, 2938, 1416, 1231, 1057, 911, 773 cm^{-1}; ^1H NMR (D_2O, 500 MHz) δ 4.03 (br s, 1H), 3.74 (dd, J = 12.0, 1.2Hz, 1H), 3.69-3.64 (m, 1H), 3.61 (dd, J = 10.5, 5.5Hz, 1H), 3.56-3.50 (m, 1H), 3.45-3.43 (m, 2H), 3.40 (dd, J = 10.5, 10.5Hz, 1H); ^{13}C NMR (D_2O, 125 MHz) δ 75.03 (CH), 70.55 (CH), 67.03 (CH), 66.75 (CH), 64.46 (CH_2), 61.31 (CH_2); MS (m/z, relative intensity): 164 (M^+, 5), 146 (13), 128 (9), 103 (38), 102 (50), 73 (100); exact mass calculated for $C_6H_{12}O_5$ (M^+): 164.0685; found 164.0685.

Example 65

Preparation of (-)-(4aR,7S,8S,8aR)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol



(4aR,7S,8S,8aR)
36%

To a solution of racemic cis-2,2-dimethyl-4,4a,6,8a-tetrahydro-pyrano[3,2-d][1,3]dioxine (52 mg. 0.30 mmol) in 4 mL of H_2O-tert-BuOH (1:1), were added sequentially $K_3Fe(CN)_6$ (312 mg, 0.90 mmol), K_2CO_3 (131 mg, 0.90 mmol), $MeSO_2NH_2$ (55 mg, 0.60 mmol) and $(DHQ)_2PHAL$ (23 mg, 0.03 mmol) at 0°C. The mixture was stirred for 5 min., OsO_4 (10 μL, 25 wt% in tert-BuOH) was added and the mixture was stirred for 64H at ambient temperature. Na_2SO_3 (100 mg) was added and the mixture was stirred for 30 min, filtered through filter paper and extracted with EtOAc-H_2O (4:1 *v/v*, 100 mL x 2). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography with 100% EtOAc.

Yield = 22 mg, 36%; colorless oil; R_f = 0.46 in EtOAc;

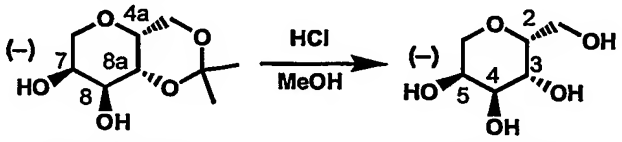
IR (neat): 3200-3600, 2976, 1747, 1185, 1111, 1024 cm^{-1};

^1H NMR (C_6D_6, 400 MHz) δ 4.00-3.95 (m, 1H), 3.90-3.80 (m, 3H), 3.63 (dd, J = 10.6, 5.5Hz, 1H), 3.56 (d, J = 2.0 Hz, 1H), 3.53-3.47 (m, 1H), 3.18 (br s, 1H), 1.47 (s, 3H), 1.14 (s, 3H);

^{13}C NMR (C_6D_6, 100 MHz) δ 98.28 (C), 69.70 (CH), 69.56 (CH), 66.31 (CH), 65.21 (CH_2), 64.80 (CH), 63.08 (CH_2), 29.57 (CH_3), 18.62 (CH_3);
MS (m/z, relative intensity): 204 (M^+, 6), 170 (19), 146 (12), 103 (42), 91 (92), 43 (100);
HRMS calculated for $C_9H_{16}O_5$ (M^+): 204.0998; found 204.0989.

Example 66

Preparation of (-)-(2R,3R,4S,5S)-2-hydroxymethyl-tetrahydro-pyran-3,4,5-triol



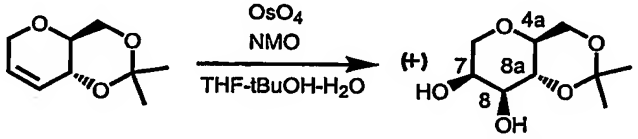
(4aR,7S,8S,8aR) (2R,3R,4S,5S)
81%

To a solution of (-)-(4aR,7S,8S,8aR)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol (22 mg, 0.10 mmol) in MeOH (2 mL) was added a solution of methanolic HCl (0.5 mL, prepared from 0.5 mL conc. HCl in 30 mL of MeOH). The solution was stirred for 1H at ambient temperature. Aqueous saturated $NaHCO_3$ (5 mL) was added and the mixture was diluted with EtOAc (50 mL). The mixture was washed with saturated $NaHCO_3$ (30 mL). The aqueous layer was washed with EtOAc (30 mL x 2). The combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*

Yield = 13 mg, 82%;
IR (neat): 3000-3600, 2944, 2913, 2891, 1460, 1380, 1296, 1114, 1024 cm^{-1}; ^1H NMR (D_2O, 500 MHz) δ 3.92-3.83 (m, 2H), 3.72-3.70 (m, 1H), 3.69-3.60 (m, 2H), 3.58-3.55 (m, 2H), 3.42 (dd, J= 10.5, 10.5Hz, 1H); ^{13}C NMR (D_2O, 125 MHz) δ 77.67 (CH), 72.15 (CH), 72.03 (CH), 67.67 (CH_2), 66.86 (CH), 63.73 (CH_2); MS (m/z, relative intensity): 164 (M^+, 2), 146 (13), 128 (9), 103 (33), 102 (26), 74 (33), 73 (81), 43 (100); exact mass calculated for $C_6H_{12}O_5$ (M^+): 164.0685; found in 164.0689.

Example 67

Preparation of (+)-(4aS,7S,8S,8aR)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol



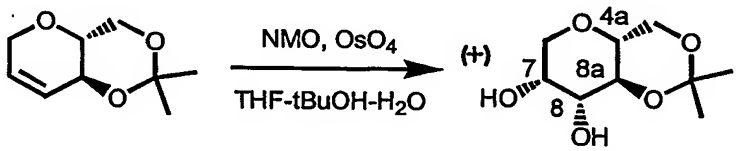
74%

To a solution of optically pure (4aS,8aR)-2,2-dimethyl-4,4a,6,8a-tetrahydro-pyrano[3,2-d][1,3]dioxine (50 mg, 0.29 mmol) in 4.5 mL of THF-tert-BuOH-H_2O (1:3:0.5) was added NMO (45 mg, 0.32 mmol) and the solution was stirred for 5 min. at ambient temperature. OsO_4 (15 µL, 25 wt% in tert-BuOH) was added and the solution was stirred at ambient temperature for 4 days. Sodiumhydrosulphite (0.2 g), Florisil (2.0 g) and H_2O (5 ml) were added and the mixture was stirred for 30 min, wash with acetone (100mL), filtered through filter paper and extracted with EtOAc (80 mL x 2). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography with 100% EtOAc.

Yield = 44 mg, 74%; optical purity = 99.0%;

Example 68

Preparation of (+)-(4aR,7S,8S,8aS)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol



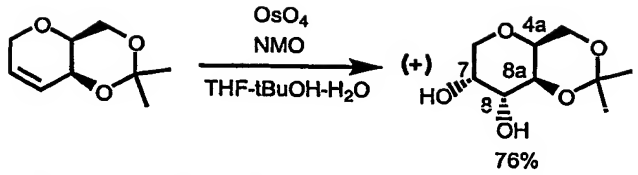
71%

To a solution of optically pure (4aR,8aS)-2,2-dimethyl-4,4a,6,8a-tetrahydro-pyrano[3,2-d][1,3]dioxine (50 mg, 0.29 mmol) in 4.5 mL of THF-tert-BuOH-H_2O (1:3:0.5) was added NMO (45 mg, 0.32 mmol) and the solution was stirred for 5 min. at ambient temperature. OsO_4 (15 µL, 25 wt% in tert-BuOH) was added and the solution was stirred at ambient temperature for 4 days. Sodiumhydrosulphite (0.2 g), Florisil (2.0 g) and H_2O (5 ml) were added and the mixture was stirred for 30 min, wash with acetone (100mL), filtered through filter paper and extracted with EtOAc (80 mL x 2). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography with 100% EtOAc.

Yield = 42 mg, 71%; optical purity = 99%

Example 69

Preparation of (+)-(4aS,7R,8R,8aS)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol



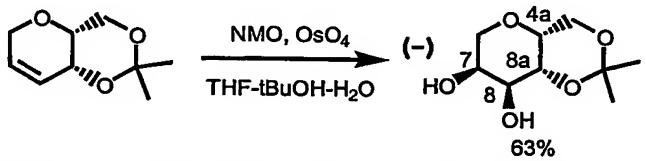
76%

To a solution of optically pure (4aS,8aS)-2,2-dimethyl-4,4a,6,8a-tetrahydro-pyrano[3,2-d][1,3]dioxine (48 mg, 0.28 mmol) in 4.5 mL of THF-tert-BuOH-H_2O (1:3:0.5) was added NMO (45 mg, 0.32 mmol) and the solution was stirred for 5 min. at ambient temperature. OsO_4 (15 µL, 25 wt% in tert-BuOH) was added and the solution was stirred at ambient temperature for 4 days. Sodiumhydrosulphite (0.2 g), Florisil (2.0 g) and H_2O (5 ml) were added and the mixture was stirred for 30 min, wash with acetone (100mL), filtered through filter paper and extracted with EtOAc (80 mL x 2). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography with 100% EtOAc.

Yield = 43 mg, 76%; optical purity = 99%

Example 70

Preparation of (-)-(4aR,7S,8S,8aR)-2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol



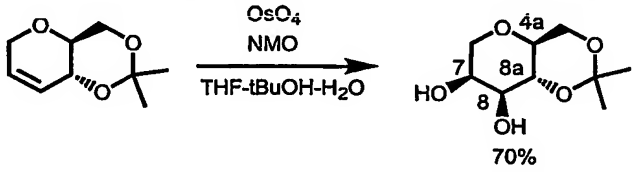
63%

To a solution of optically pure (4aR,8aR)-2,2-dimethyl-4,4a,6,8a-tetrahydro-pyrano[3,2-d][1,3]dioxine (50 mg, 0.29 mmol) in 4.5 mL of THF-tert-BuOH-H_2O (1:3:0.5) was added NMO (45 mg, 0.32 mmol) and the solution was stirred for 5 min. at ambient temperature. OsO_4 (15 µL, 25 wt% in tert-BuOH) was added and the solution was stirred at ambient temperature for 4 days. Sodiumhydrosulphite (0.2 g), Florisil (2.0 g) and H_2O (5 ml) were added and the mixture was stirred for 30 min, wash with acetone (100mL), filtered through filter paper and extracted with EtOAc (80 mL x 2). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography with 100% EtOAc.

Yield = 37 mg, 63%; optical purity = 99%

Example 71

Preparation of 2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine-7,8-diol



70%

To a solution of 2,2-dimethyl-4,4a,6,8a-tetrahydro-pyrano[3,2-d][1,3]dioxine (50 mg, 0.29 mmol) in 4.5 mL of THF-tert-BuOH-H_2O (1:3:0.5) was added NMO (45 mg, 0.32 mmol) and the solution was stirred for 5 min. at ambient temperature. OsO_4 (15 μL, 25 wt% in tert-BuOH) was added and the solution was stirred at ambient temperature for 4 days. Sodiumhydrosulphite (0.2 g), Florisil (2.0 g) and H_2O (5 ml) were added and the mixture was stirred for 30 min, wash with acetone (100mL), filtered through filter paper and extracted with EtOAc (80 mL x 2). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography with 100% EtOAc.

Yield = 41 mg, 70%.

IR (neat): 3000-3600, 2952, 1473, 1268, 1161, 1087, 1021 cm^{-1};

^1H NMR (C_6D_6, 400 MHz) δ 3.80-4.00 (m, 3H), 3.75 (dd, J = 13.2, 13.2Hz, 1H), 3.53 (br s, 1H), 3.35-3.42 (m, 1H), 2.90-3.00 (m, 2H), 2.50 (br s, 1H), 1.44 (s, 3H), 1.24 (s, 3H);

^{13}C NMR (C_6D_6, 100 MHz) δ 99.86 (C), 72.65 (CH), 72.14 (CH), 72.03 (CH), 70.29 (CH_2), 69.68 (CH), 62.30 (CH_2), 29.47 (CH_3), 19.12 (CH_3); MS (m/z, relative intensity): 186 (M^+-18, 6), 170 (7), 141 (3), 128 (36), 115 (42), 95 (91), 84 (100).

Although the invention has been described with reference to the above examples, it will be understood that modifications and variations are encompassed within the spirit and scope of the invention. Accordingly, the invention is limited only by the following claims.